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OPEN WOUNDS OF THE HAND*

J. Edward Flynn, M.D.†

BOSTON

THAT trauma to the hand is of great importance from an economic point of view can be understood from statistics collected from the National Safety Council and state industrial commissions. In 1952 there were 9,620,000 accidental injuries in the United States, of which about 2,000,000 were occupational accidents. The total estimated cost was $8,700,000,000, of which $2,900,000,000, or a third, represented the cost of occupational accidents[1] (Table 1). Of the 2,000,000 occupational accidents in 1952 about a third involved the hand and the arm. Averages for other years[2] are similar (Table 2).

TABLE 1. *Injuries in 1952.*

Type	Number	Percentage
Occupational	2,000,000	20.8
Motor-vehicle (Nonoccupational)	1,270,000	13.2
Home accidents	4,300,000	44.7
Public accidents (excluding occupational and motor-vehicles)	2,050,000	21.3
Total	9,620,000	

Requirements for the return of maximum function after injuries to the hand are as follows: freedom from infection; proper surgical repair of wounded tissues; and prevention and elimination of contractures.

Prevention of Infection

Careful attention to such details as proper first-aid therapy, an accurate history, initial inspection with the surgeon's nose and mouth masked, adequate physical examination before exploration of the depths of the wound, antitetanus therapy, adequate local shaving and cleansing, proper irrigation and débridement of the wound and the prophylactic use of antibiotics are the first steps in the prevention of infection.

The surgeon's first therapeutic decision is whether to perform a primary or a delayed reconstruction of the injured hand in question. Five facts help in this decision: knowledge of the causative agent, the circumstances of the injury, the type of first aid rendered and the time that has elapsed between the injury and the surgeon's examination. For example, a primary reconstruction can usually be performed when the injury has been caused by a sharp instrument such as a knife, occurring indoors and to a clean hand, when a sterile pressure dressing and splint have been applied by experts and when the lapse of time between the injury and the dressing is short. On the other hand, when a crushing agent outdoors is involved, when the hand is dirty and untrained per-

TABLE 2. *Occupational Injuries, according to Part Involved.*

Source	Period	Total Injuries	Injuries of Upper Extremity	
			Number	Percentage
Massachusetts Industrial Commission[3]	yr. 3 (1948-50)	170,002	60,252	35.4
Connecticut Industrial Commission[4]	3 (1950-52)	52,445	19,764	37.6
New York Industrial Commission[5]	2 (1949-50)	212,843	76,630	36.0
Illinois Industrial Commission[6]	4 (1949-52)	176,530	75,860	31.6
California Industrial Commission[7]	3 (1950-52)	428,112	133,612	31.8
National Safety Council[1]	1 (1952)	2,000,000	680,000	34.0

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†Assistant clinical professor of surgery, Tufts College Medical School; assistant visiting surgeon, First Surgical Service, Boston City Hospital; attending surgeon, Veterans' Administration Hospital; visiting surgeon, St. Elizabeth's Hospital.

sonnel have attempted to apply first aid and when many hours have elapsed from the time of injury to definitive therapy, a delayed reconstruction will be necessary.

Whatever the decision concerning the propriety of immediate or delayed reconstruction, certain basic requisites must be met by the first examination. These have a direct bearing on the occurrence of later infection.

The initial inspection of the wound will determine its exact location, its state of cleanliness, its type and its superficial extent. A sterile dressing is then applied. The extent of damage to tendons, nerves and bones is then determined so that this part of the diagnosis is made before the depths of the wound are investigated at operation. X-ray films are taken, if necessary, and the patient is immediately removed to the operating room.

With the patient ready for definitive surgery, the influence of the time that has elapsed since the injury was inflicted is evaluated. The time factor must be considered from the point of view of the probable lethal effects it may have had on subsequent repair processes and as such is only one — but perhaps the most important — of other characteristics of the wound, all of which are interlocking and all of which must be included in this preoperative estimation.

For example, before the antibiotics were introduced six hours from time of injury to operation was considered the limit within which to perform a primary repair of any exposed tendons in open wounds of the hand, and two hours was the orthodox time limit for primary repair of the flexor tendons within sheaths. The six-hour limit was based on experiments entailing demonstration of the amount of gross contamination of the wound and the smearing of dirt on the thighs of guinea pigs, as well as the clinical experience of wounds and various repairs in World War II. In crushed or avulsed wounds primary repair of tendons may be hazardous, whereas in a cleanly incised wound with minimal tissue injury or contamination, tendons can be repaired safely, even after considerable time has elapsed. With careful selection and in questionable cases, when a smear from the wound does not show either cocci or an excess of leukocytes, primary operative repair with wound closure is frequently successful up to twelve or even twenty-four hours in some cases. Beyond twenty-four hours the chances favor severe infection. Primary repair should never be attempted in wounds caused by human or animal bites or in those contaminated by human or animal excreta. Chemotherapy is considered of value in increasing this time factor, and, consequently, 50,000 units of penicillin is given postoperatively every four hours for at least three days in severe injuries.

In Table 3, wounds of the hand are classified according to the types encountered over a five-year period at the Boston City Hospital.

TABLE 3. *Classification of Compound Wounds of the Hand.**

TYPE OF WOUND
Incised:
Clean inside or outside sheath
Dirty inside or outside sheath
Crushed:
Clean inside or outside sheath
Dirty inside or outside sheath
Avulsed:
Clean inside or outside sheath
Dirty inside or outside sheath
Specific types:
Involving finger tip (no bone exposed or with bone exposed)
Finger (involvement of flexor or extensor surface)
Glove avulsion of fingers or hand
Volar or dorsal aspect of hand
Volar and dorsal aspects
Late:
Clinical signs of redness and edema (smear showing cocci or increased leukocytes)
Delayed (crushed, incised or avulsed)
Septic

*Based on Flynn.[8]

SURGICAL TREATMENT

Nerve Repair

A primary repair is made of incised nerves in all types of wounds except those that are grossly septic. Avulsed and crushed nerves are best treated by early delayed repair, three to six weeks after injury.

Fractures

These are reduced by immediate manipulation in all types except grossly septic wounds, in which fractures are reduced by gradual traction.

Further decision regarding reconstruction must await detailed knowledge of the amount and type of damage to the structures in the depth of the wound. For this purpose anesthesia of the part and medicinal sterilization of the wound and adjacent areas are essential.

Anesthesia

A brachial-block anesthesia, with xylocaine, is used for adults with extensive injuries requiring three or more hours of operating. Block of individual nerves may be used for simple cases in which the operation does not exceed two hours, and when it is not necessary to use a tourniquet for hemostasis. The median and radial nerves are usually blocked just above the wrist, and the ulnar nerve at the elbow (occasionally at the wrist). Epinephrine in novocain should never be injected into a finger because of the risk of gangrene.[9]

Sterilization

In open wounds of the hand and wrist all surfaces of the upper extremity are shaved from elbow to finger tips to avoid contamination. The same area is scrubbed for ten to twenty minutes with pHisoderm.

Cotton gauze is used for cleansing; brushes are avoided. Irrigation, performed with the injured part on a sterile modified Bryant irrigating pan, aids in converting a contaminated wound into a clean surgical one.[10] Débridement should consist of the removal of foreign bodies, an excision of the entire surface of the wound for a depth of 2 mm. and the removal of all devitalized and contaminated tissue.

Repair of open wounds of the hand should never be performed in an office or on an accident floor but always in a well equipped operating room with proper lighting and adequate assistance. A pneumatic cuff on the arm provides hemostasis. The use of sterile finger cots eliminates contamination from the patient's fingernails. No. 000 or 00000 plain catgut is employed for ligatures. Nerves are sutured with No. 00000 silk on an atraumatic needle or with fine tantalum wire. Tendons may be repaired with stainless-steel wire, silk or cotton but never with catgut. One closes the wounds by suturing without tension, to prevent necrosis, or by skin grafting.

Antitetanus serum is given for all extensive open wounds of the hand and for any others that are thought to be favorable for the growth of tetanus. A skin test is performed, and if the patient is not sensitive, 1500 units is given with a similar dose repeated in ten days or at a subsequent operation. Many investigators disagree on the duration of active immunity after tetanus toxoid. Others disagree on whether tetanus toxoid and antitoxoid should be used simultaneously. Active immunity from tetanus toxoid appears to last about ten years. If toxoid has recently been given to the patient the serum is omitted, and a stimulating dose of 1 cc. given. In patients who have had previous injections of tetanus toxoid the simultaneous use of antitoxoid and recall injections of tetanus toxoid is indicated when the following conditions are present: delay in prophylaxis, multiple wounds, debility from various causes or great loss of blood.[11]

With these preparations made the surgeon can explore the wound in detail and decide, as the result of these findings and the data collected earlier, just what form of surgical therapy promises the best results. After freedom from infection has been assured so far as possible, the objects are to attain proper surgical repair and the prevention and, in older wounds, elimination of contractures. For these purposes it is profitable to classify the wounds as incised, avulsed, crushed and late or grossly septic.

Incised Wounds. With clean incised wounds it is estimated that primary closure of the wound may be attempted up to twenty-four hours after injury provided that there is no sign of inflammation or that, in questionable cases, a smear of the wound shows no increase in leukocytes and no cocci. With lacerated tendons without sheaths the attempt at primary repair of the tendons may be made twenty-four hours after injury only under ideal circumstances. However, with injuries to tendons with intact sheaths, primary repair of the tendons may be carried out up to twelve hours after injury, provided the wound is clean. In the last five years 303 cases of clean, incised, open wounds involving tendons without sheaths have been treated on the Hand Surgical Service of the Boston City Hospital.

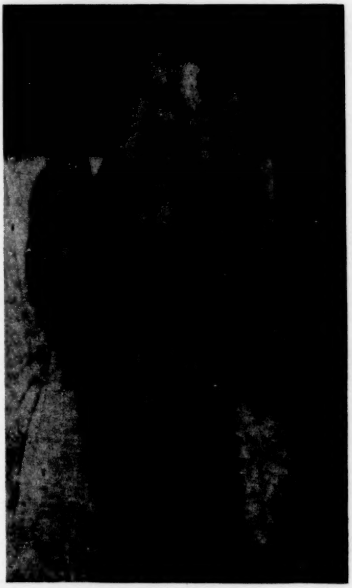


FIGURE 1. *Incised Open Wound of the Wrist, with Successful Primary Reconstruction and Closure Fourteen Hours after Injury (Reproduced from Flynn[12] with the Permission of the Publishers).*

These patients were operated on one to twenty-four hours after injury. There were 6 cases in which postoperative sepsis occurred. All 6 patients had multiple tendon and nerve injuries; operation was performed within six hours in each case (Fig. 1).

There were 84 patients with clean, incised wounds involving tendons within sheaths in whom primary tenorrhaphy was performed. These patients were operated on within twelve hours of injury. Eight patients were operated on between the eleventh and the twelfth hour. There was no postoperative sepsis in any case.

There were 36 patients with dirty, incised wounds involving tendons without sheaths in whom débridement was complete and primary tenorrhaphy was performed. These patients were operated on one to six hours after injury. There was no sepsis after operation.

In 6 cases of dirty, incised wounds, involving tendons within sheaths, débridement was complete, and primary tenorrhaphy was performed. These patients were operated on one to five hours after injury. There was no postoperative sepsis.

Open wounds often need enlargement for retrieving foreign bodies or because of retracted tendons

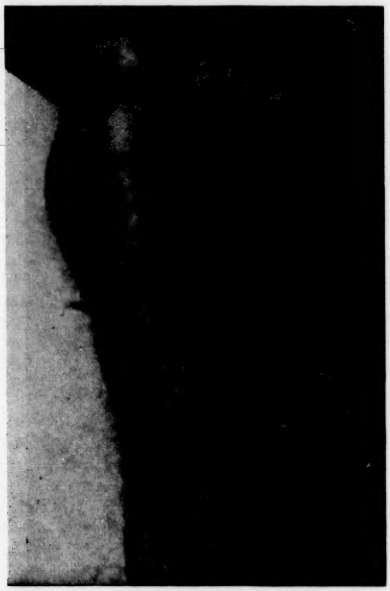


FIGURE 2. *Complete Operation on the Severe, Incised Wound shown in Figure 1 (Reproduced from Flynn" with the Permission of the Publishers).*
The enlarging incision was made over the lateral aspect of the wound.

and nerves. One should not enlarge an oblique or transverse wound by cutting from its center and thus making a T-shaped or arrow-shaped wound. Enlargement should be obtained by one incision proximalward from one end of the transverse wound and another distalward from the other end; this gives good exposure and good flaps to cover the underlying reconstructed tendons and nerves. Enlarging incisions, however, should never cross flexion creases at right angles. The use of a short proximal transverse incision often suffices to retrieve a retracted tendon. Figure 2 shows the completed operation on the severe, incised wound demonstrated in Figure 1. The enlarging incision to retrieve retracted tendons was made from the lateral aspect of the wound.

With dirty or greatly devitalized, incised wounds in which débridement is incomplete, delayed closure and later reconstruction are performed. When all dirt and devitalized tissue cannot be completely excised or when too much time has elapsed between injury and admission to the hospital the wound should be packed with a sparsely covered petrolatum gauze, and a sterile dressing and cast applied. Antibiotics, usually penicillin, are given for four days. The dressing is then removed if the patient's temperature is normal; if a culture of the wound shows no growth closure by suturing or skin grafting is performed. Sepsis, granulations and contractures are all diminished by early closure of the wound.

Avulsed wounds. With clean, avulsed wounds in which there is no sign of inflammation a primary closure of the wound may be performed up to twelve hours after injury. With such wounds avulsed tendons are usually not repaired primarily except that in some cases a cleanly lacerated tendon outside a sheath may

FIGURE 3. *Avulsed Wound of the Finger Tip, with Bone Involved (Reproduced from Flynn" with the Permission of the Publishers).*
A pedicle graft from the thenar eminence will cover the defect on the finger. A split-thickness graft covers the defect in the thenar area.

be repaired up to twelve hours and a cleanly lacerated tendon within a sheath up to six hours from time of injury. In this series there were 89 cases of clean, avulsed wounds involving tendons outside sheaths, and 4 cases involving tendons within sheaths. Primary closure and repair were performed in 85 of these cases, with postoperative sepsis in 3.

With dirty, avulsed wounds in which débridement is incomplete no attempt is made at primary tendon repair; closure is delayed.

Avulsed wounds of finger tips with no bone exposed are treated by primary closure with an inter-

mediate-thickness skin graft. With avulsed wounds of finger tips involving bone, however, it is important to crush and transect the digital nerves about 2 cm. proximal to the original wound and fix the ends of the nerves in bone or subcuticular tissue. The defect on the tip of the finger may then be covered by either a full-thickness or a pedicle skin graft. When the former is used the sutures at each of the four angles of the graft are tied over a piece of fitted sponge rubber to prevent hematoma formation. A pedicle graft, which is probably more satisfactory, should be cut from the thenar eminence of the same hand and may be used for the tips of the index, middle and ring fingers, from the hypothenar eminence when the little finger is involved and from the dorsum of the middle phalanx of the index or middle fingers when the thumb is involved. The donor site of the pedicle graft is covered with an intermediate-thickness skin graft. Immobilization of the hand in a plaster cast is maintained for two weeks, and then the graft is detached (Fig. 3).

Although an intermediate-thickness skin graft may be sutured directly to the bone stump of a partially amputated finger, this usually leaves a tender stump that requires later reconstruction.

An avulsed wound over the volar aspect of a finger may be covered with a full-thickness free skin graft by a graft from one or both sides of the finger, or by a pedicle graft from the dorsum of an adjoining finger or the abdomen. An avulsed wound over the dorsum of a finger may be covered by an intermediate-thickness graft, a full-thickness graft or a primary pedicle graft from the abdomen (Fig. 4).

Occasionally, a glove avulsion of the skin of a finger or hand occurs. Such an injury is best treated with a fresh skin graft rather than reapplication of the avulsed skin, which increases the chances of infection; with a great supply of other skin suitable for grafting it is safer to apply freshly cut grafts for glove avulsions. A tubular pedicle graft can then be prepared to replace the skin graft later.

If the recipient site is avascular and will not take a free skin graft a primary pedicle or pocket graft from the abdomen may be used—but only when absolutely necessary, because the susceptible fat may become infected and thrombosis may occur. A free graft will usually not grow on a recipient site if the bone is devoid of periosteum, the tendons devoid of tendon sheaths and the nerves exposed, or if there is an avascular bed.

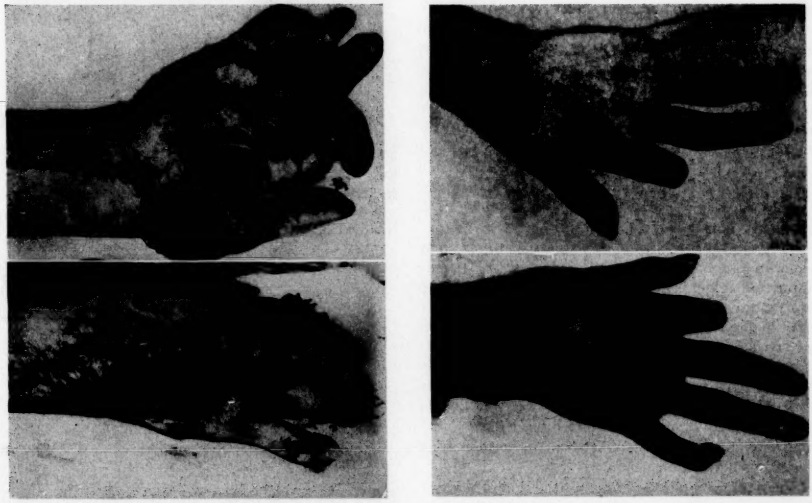
Extensive avulsed wounds over the volar or dorsal surface of the hand are preferably treated by the temporary split-graft method, with later application of tubular pedicle grafts. In some cases, however, it is necessary to apply a primary pedicle graft. In others it may be better to apply a split-thickness graft over the dorsum and a primary abdominal pedicle graft over the volar aspect. A primary pedicle graft to both surfaces is rarely indicated and, in any event, is technically difficult.

Crushed wounds. Primary closure of clean, crushed, open wounds may be performed up to twelve hours from the time of injury when there is no sign of inflammation, but crushed tendons should never be repaired primarily. A cleanly incised tendon outside a tendon sheath in such a wound, however, may be primarily repaired up to twelve hours, and an incised tendon within a sheath up to six hours after injury. In this series there were 26 cases of clean, crushed, open wounds involving tendons outside sheaths. Primary closure or reconstruction was performed in 25 of these cases, without postoperative sepsis. There were also 2 cases of clean, crushed wounds involving tendons still within their sheaths in which primary repair was done within four hours, without later sepsis.

FIGURE 4. *Avulsed Wound of the Skin, Tendon and Bone Cortex and Marrow* (A), *with Generous Primary Pedicle Grafting to Facilitate Later Reconstruction (Reproduced from Flynn[4] with the Permission of the Publishers).*

Primary closure of dirty, crushed wounds in which débridement is complete may be performed up to eight hours after injury. Cleanly incised tendons usually can be primarily reconstructed up to six hours

from the time of injury. Crushed tendons should not be repaired primarily. In this series of dirty, crushed wounds with complete débridement, there were 30 cases involving tendons outside their sheaths and 1 case involving tendons within their sheaths. Primary closure or reconstruction was performed in 29 of these cases, with no postoperative sepsis. (Fig. 5*A*). This patient, who was first seen eight hours after injury, presented a problem in the primary treatment of the wounds rather than one of primary reconstruction. Figure 5*B* shows that the same wounds healed by first intention after proper cleansing, irrigation, débridement, suturing and grafting. Reconstruction was performed later.



A B

FIGURE 5. *Severely Crushed, Dirty, Compound Wounds, Showing Appearance Eight Hours after Injury* (A) *and When Proper Irrigation, Débridement and Skin Coverage Had Been Done* (B), *with Healing by First Intention (Reproduced from Flynn*[13] *with the Permission of the Publishers).*

With dirty, crushed, open wounds in which complete débridement is not possible no primary reconstruction is attempted, and a delayed closure of the wound is performed.

Late and septic wounds. After twelve to twenty-four hours, depending on the type of injury, or if a smear of the wound shows cocci or increased leukocytes, the wound is classed as late. Bacteria will have multiplied and penetrated into the tissues around the wound. The opportunity for débridement, and hence of repair of the deep structures and closure of the wound, has passed because of the virtual certainty of resultant infection after such procedures.

Postoperative Treatment

A pressure dressing and splinting, if properly applied, control ooze, prevent hematoma and provide local rest. Rest in bed enhances the prevention of infection and the healing of traumatized tissues. Elevation of the limb, with the wrist suspended from an irrigating stand, prevents edema, hematoma and thrombosis.[14]

Motions should not be instituted until the wound is healed. Active motions are begun three weeks after flexor-tendon repair and five weeks after extensor-tendon repair. Motion such as that against the resistance of a rubber ball, a sponge or bouncing putty aids in the restoration of function. Whirlpool baths encourage circulation. Dynamic splints help to overcome some of the soft-tissue contractures and fixation of joints.

When contractures occur with conservative therapy, however, secondary reconstruction of the injured area must be performed. All skin and soft-tissue scar must be excised. The resultant defect is then closed with split-thickness, whole-thickness or pedicle skin graft. Paratenon graft about a suture site may aid in the restoration of gliding to a tendon, and tendon grafting may be necessary to restore function.

Preliminary reports indicate that hydrocortisone or compound F is of no value in helping the gliding of a primarily reconstructed tendon but may be of use in decreasing the formation of adhesions in some secondary repairs.[15]

Results

Previous reports indicated how much antibiotics were thought to have increased the time factor for safely operating on open wounds of the hand.[8,12,13] In this report I have excluded uncomplicated compound fractures and have included only the wounds with complete tendon or nerve involvement.

TABLE 4. *Incidence of Sepsis in Open Wounds of the Hand.*

Year	No. of Cases	Cases of Sepsis
1	116	1
2	110	2
3	122	2
4	126	2
5	138	2
Totals	612	9 (1.47%)

The results in 612 patients with open wounds of the hand seen at the Boston City Hospital over a five-year period (Table 4) indicate that this estimate of the increase in the time the surgeon is now permitted for delay between injury and operation is considerably longer than the six-hour limit before antibiotics were available.

Conclusions

In the successful treatment of open wounds of the hand one must thoroughly understand the importance of the multitude of details necessary to avoid infection and to aid proper tissue repair and elimination of contractures. There is a close interrelation between many of the details of these three factors. The time limit from injury to operation appears to be increased since the advent of antibiotics; an incidence of sepsis of 1.47 per cent in 612 cases seen over a five-year period substantiates this estimate.

To solve the principal remaining problems—control of fibrosis and contractures—the technic must be atraumatic, and hematomas must be prevented by adequate ligations, pressure dressings and occasionally the use of a drain. The minimum use of nonabsorbable suture and ligature material is essential to avoid fibrosis. Generalized and local rest, with elevation of the hand, help decrease scar formation. Active and active resistive motions and whirlpool baths aid restoration of function. Dynamic splints may overcome some joint contractures and some contractures caused by scar tissue. Preliminary reports indicate that hydrocortisone is of no value in primary reconstruction but may be of value in preventing contractures and in secondary reconstructions.

I am indebted to Dr. Donald Munro for constructive criticisms and suggestions.

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ORAL ADMINISTRATION OF A POTENT CARBONIC ANHYDRASE INHIBITOR ("DIAMOX")*

II. Its Use as a Diuretic in Patients with Severe Congestive Heart Failure

ARNOLD S. RELMAN, M.D.,† ALEXANDER LEAF, M.D.,‡ AND WILLIAM B. SCHWARTZ, M.D.§

BOSTON

IN a preceding paper[1] the metabolic effects of a new potent carbonic anhydrase inhibitor ("Diamox") were reported. In patients with congestive heart failure oral administration of this compound regularly resulted in excretion of an alkaline urine containing increased amounts of potassium and sometimes increased quantities of sodium.

The present study was undertaken to evaluate the clinical efficacy of Diamox as a diuretic in patients with severe congestive heart failure. The action of the drug in patients with respiratory acidosis and congestive heart failure due to chronic cor pulmonale is the subject of another report.[2]

METHODS AND MATERIALS

Twenty-six patients with severe congestive heart failure and varying degrees of peripheral and pulmonary edema were studied during twenty-eight trials of the drug.¶ All patients had been in failure for at least several months and, with only 3 exceptions, had been under continuous treatment with digitalis, mercurial diuretics and salt restriction before hospitalization. All patients were observed in the hospital at bed rest. The drug was given only after a control observation period of usually a week or more had indicated stabilization of weight and of the signs of congestive heart failure. During the control period most of these patients were given one or more injections of mercurial diuretics, and many were found to be refractory. All diuretics were discontinued at least two days before the trial of Diamox, and no treatment besides digitalis and salt restriction was used during the course of therapy. In many patients mercurial diuretics were tried again after Diamox had been discontinued.

Observations included frequent clinical evaluation of signs and symptoms, daily weighing, determination of blood nonprotein nitrogen and electrolyte concentrations before and after treatment and usually measurement of urine and blood pH. The drug was administered orally in varying dosage schedules for total periods of three to twelve days, with an average treatment period of six days. When weight loss occurred the drug was discontinued only after the patient had clearly ceased to respond to further therapy.

RESULTS

Table 1 summarizes the data. There were 10 cases of hypertensive heart disease, 7 of rheumatic heart disease, 6 of arteriosclerotic heart disease, 2 of unusual types of aortic insufficiency (1 with Marfan's syndrome, and 1 with a ruptured valve after acute bacterial endocarditis), and 1 of syphilitic heart disease. The ages ranged from twenty-nine to seventy-three years. In 2 patients (Cases 4 and 5) congestive heart failure was complicated by hyperuricemia with uric acid calculi and crystalluria.

Twenty-three courses of therapy were preceded by a trial of mercurial diuretics, and in 16 cases there was no weight loss. In 5, there was a loss of 2 or 3 pounds with mercury, and 2 patients lost 7 to 9 pounds. Fourteen patients had blood nonprotein nitrogen concentrations below 50 mg. per 100 cc., and 12 had concentrations of 50 to 100 mg. per 100 cc. Five patients had a hypochloremic alkalosis, with a blood bicarbonate level higher than 32 milliequiv. per liter, and 2 had mild metabolic acidosis; the others had normal bicarbonate levels. In 4 cases the serum sodium concentrations were below 130 milliequiv. per liter.

The total diuretic response to the course of therapy with Diamox is summarized in Table 2. Approximately half the patients failed to lose weight. The majority of the others had only small diureses (loss of 2 to 6 pounds). One patient lost 11 pounds over a period of nine days and was edema free at the end of that time. Most patients had a definite pharmacologic effect from the drug even when there was little or no diuretic response (Table 1). Only 3 failed to show either a rise in urine pH or a fall in serum carbon dioxide content. Among those who lost more than 3 pounds there was no quantitative relation between the magnitude of the diuresis and the fall in serum carbon dioxide content.

*From the medical services, Evans Memorial, Massachusetts Memorial Hospitals, Massachusetts General Hospital and New England Center Hospital, and the departments of medicine, Boston University School of Medicine, Harvard Medical School and Tufts College Medical School. Supported in part by grants from the National Heart Institute of the National Institutes of Health, United States Public Health Service, the American Heart Association, the Greater Boston and Worcester District chapters of the Massachusetts Heart Association, and Lederle Laboratories Division of the American Cyanamid Company.

†Assistant professor of medicine, Boston University School of Medicine; associate member, Evans Memorial, Massachusetts Memorial Hospitals.

‡Associate in medicine and Howard R. Hughes Fellow in Medicine, Harvard Medical School; assistant physician, Massachusetts General Hospital.

§Assistant professor of medicine and Markle Scholar in Medical Sciences, Tufts College Medical School; assistant physician, New England Center Hospital.

¶Supplied through the courtesy of Dr. J. M. Ruegsegger, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York, and Drs. R. O. Roblin and T. H. Maren, Chemotherapy Division, Stamford Research Laboratories, American Cyanamid Company, Stamford, Connecticut.

In no case did the serum bicarbonate level fall below 17 milliequiv. per liter. The serum potassium was slightly decreased after therapy in most cases but was never below 3.3 milliequiv. per liter. No signs or symptoms of potassium depletion were noted. The major side effect observed was drowsiness, which was seen in 9 cases. This reaction seemed to be related to dosage because it was never encountered in patients receiving 500 mg. or less per day. In 1 patient receiving 500 mg. per day transient digital and circumoral paresthesias developed.

In 13 courses of treatment the drug was given at regular intervals of four to eight hours, total dosage ranging from 0.75 gm. to 3 gm. per day. In the other 15 studies Diamox was administered once daily in a dose of 250 or 500 mg. Within this range of dosage schedules there was no relation between the size or frequency of the dose and the total therapeutic effect.

Only 3 of the 13 courses of treatment in patients with blood nonprotein nitrogen concentrations of 50 mg. per 100 cc. or above resulted in weight loss of 4 pounds or more. By contrast 7 of the 15 courses of therapy in nonazotemic patients effected diureses with weight loss of 4 or more pounds. Of the 4 patients with a serum carbon dioxide content higher than 32 milliequiv. per liter and a normal nonprotein nitrogen, 2 had slight diureses, and 2 lost no weight at all.

Of 16 patients who had been unresponsive to mercurial diuretics before treatment with Diamox 11 were given another trial of mercurial therapy immediately after the end of treatment with Diamox. Five of these patients now responded with diureses (weight loss of 3 pounds or more) to the first dose of mercury.

Although, with 1 exception, edema was not well controlled by Diamox many of these patients were subsequently managed satisfactorily with other measures. Eleven patients lost 10 to 30 pounds (average of 17) with mercurial diuretics alone or in combination with ammonium chloride or intravenous injection of aminophylline. Previous weight loss with Diamox in this group was only 2 pounds. Six patients failed to respond well to any of the diuretics tried.

Discussion

The patients included in this study had congestive heart failure severe enough to require hospitalization, and many of them had become resistant to mercurial diuretics. Although one would not choose such a group to demonstrate the optimal effects of a new diuretic agent it is in this group that such an agent is most urgently needed.

The results of therapy with Diamox were disappointing. In only 1 case did it prove to be a clinically effective diuretic agent in the over-all management of these edematous patients. Approximately half the group lost no weight, and, in the others, diuresis was so small or so gradual as to be of scant benefit. Because of the length of time over which these small diureses developed it is difficult even to be certain that they were always attributable to the drug.

More favorable results with Diamox have been reported by Friedberg and his associates,[3] who gave short courses of therapy to a small group of hospitalized patients. The results of their study are difficult to evaluate because, in the first place, control periods were inadequate (0 to 2 days) and, secondly, "good" or "excellent" clinical responses were claimed in 9 of the 11 patients who had an average weight loss of only 4.4 pounds over the entire course of treatment.

Some of the patients in the present series were apparently made more responsive to mercury by treatment with Diamox, for 5 who had previously been unresponsive to mercurial diuretics lost 3 pounds or more when retreated with mercurial agents immediately after Diamox had been stopped. Such results are not unexpected since the acidifying effects of Diamox are similar to those of ammonium chloride although less intense. With the latter drug, however, it is usually possible to achieve mercurial diuresis more effectively and consistently.

The relative ineffectiveness of Diamox, even in patients in whom some weight loss was obtained, is emphasized by the fact that many patients responded quite satisfactorily to subsequent intensive therapy with mercurial diuretics, ammonium chloride or intravenous injection of aminophylline used in various combinations. Thus, the majority of the group of cases were not totally resistant to intensive diuretic therapy.

The experiments of Maren, Wadsworth and Yale[4] on dogs suggested that treatment with a single daily dose would permit regeneration of plasma bicarbonate in the drug-free intervals and thus avoid the development of acidosis. However, in half our patients, who were given only one dose a day, there was no significant improvement in results, and in 8 cases significant reductions in bicarbonate nevertheless appeared. These results might have been predicted from some of the experiments reported in the preceding study, in which a twenty-four-hour interval between doses was not adequate to permit complete restoration of responsiveness to the metabolic effects of Diamox.[1] Longer intervals between doses — for example, seventy-two hours — might be adequate for this purpose, although no data are available on this point. However, even in such circumstances, it is clear that a drug such as Diamox, which produces at most a weight loss of 1 or 2 pounds per single dose, given at these relatively infrequent intervals, could hardly be of value in the management of hospitalized patients in severe congestive heart failure.

The importance of renal function as a measure of response to Diamox is emphasized by the fact that only 3 of 13 courses of treatment in azotemic patients resulted in weight loss of 4 pounds or more,

TABLE 1. *Effect of Diamox in 26 Cases of Congestive Heart Failure.*

						Chemical Constituents Before Treatment					Diamox Treatment	
Case No.	Sex	Age yr.	Diagnosis	Duration Failure yr.	Weight Lost with Last Dose of Mercurial Diuretic lb.	Nonprotein Nitrogen mg./100 cc.	Sodium milliequiv./liter	Potassium milliequiv./liter	Carbon Dioxide milliequiv./liter	Chloride milliequiv./liter	pH	Dose	Duration days
1	M	63	Hypertensive heart disease	¼	0	32	138	5.2	31.9	99	7.40	1-3 gm. every 24 hr.	11
2	M	67	Hypertensive & arteriosclerotic heart disease	5	0	95	139	5.8	26.0	102	7.40	500 mg. 5 times a day	7
3	F	49	Rheumatic heart disease; aortic & mitral stenosis & insufficiency; atrial fibrillation.	5	0	40	136	4.5	34.0	92	—	500 mg. every 8 hr.	4
4	M	66	Aortic insufficiency following acute bacterial endocarditis; uric acid crystals in urine.	1	0	53	127	5.9	24.0	97	—	500 mg. every 8 hr.	12
5	M	63	Arteriosclerotic heart disease; uric acid crystals in urine.	1	1	82	130	10.4	28.0	101	7.37	250 mg. every 6 hr.	12
6	M	38	Hypertensive heart disease	½	0	34	131	3.6	35.3	90	—	500 mg. every 6 hr.	8
7	M	60	Rheumatic heart disease, with aortic insufficiency & cirrhosis	½	0	42	131	4.9	26.0	90	7.37	500 mg. every 8 hr.	3
8	M	64	Hypertensive & arteriosclerotic heart disease, with atrial fibrillation	2	9	52	140	5.5	27.0	105	—	500 mg. every 8 hr.	5
9	M	73	Arteriosclerotic heart disease, with atrial fibrillation	3	0	80	126	4.7	29.0	90	7.45	500 mg. every 8 hr.	5
10	F	60	Hypertensive heart disease	½	0	58	137	4.9	40.0	84	—	250 mg. every 6 hr.	4
11	M	30	Hypertensive heart disease	4-5	0	86	138	5.3	27.3	92	—	250 mg. every 8 hr.	6
12	M	52	Hypertensive heart disease, with atrial fibrillation	4	2	22	136	4.9	26.2	106	—	500 mg. every 24 hr.	9
13	M	67	Calcific aortic stenosis; rheumatic heart disease.	2	2	54	—	—	27.1	98	—	250 mg. every 24 hr.	3
14	F	56	Hypertensive cardiovascular disease; nephrosclerosis.	6	Not tested	70	—	—	28.0	90	—	250 mg. every 24 hr., then 500 mg. every 24 hr.	3 2
15	F	29	Aortic insufficiency (Marfan's syndrome)	1/10	0	23	131	—	34.0	87	7.39	500 mg. every 24 hr.	4
16	M	55	Hypertensive heart disease	2	Not tested	40	143	4.4	33.0	98	—	250 mg. every 2-3 days	8
17	M	36	Rheumatic heart disease; atrial fibrillation.	6	7	25	134	5.0	28.0	93	7.40	250 mg. every 24 hr.	8
			Same patient 3 mo. later	6¼	0	28	138	4.1	24.0	108	—	500-750 mg. every 24 hr.	5
18	M	69	Arteriosclerotic heart disease	5	3	47	133	5.4	27.0	101	7.38	250 mg. every 6 hr.	3
19	M	50	Rheumatic heart disease, with mitral stenosis	3	3	62	137	3.6	26.0	94	7.42	250 mg. every 24 hr.	5
20	F	52	Rheumatic heart disease, with mitral stenosis	5	3	38	141	5.6	32.0	98	—	250 mg. every 24 hr. plus 4.8 gm. of potassium chloride	7
21	M	61	Hypertensive cardiovascular disease	½	Not tested	100	137	3.3	26.0	96	—	250 mg. every 6 hr.	4
			Second admission 9 mo. later	1¼	0	90	137	4.4	25.0	94	7.30	250 mg. every 24 hr.	4
22	M	57	Syphilitic heart disease; aortic & tricuspid regurgitation.	3	0	70	129	5.1	26.0	88	—	250 mg. every 24 hr.	3
23	F	56	Rheumatic heart disease; atrial fibrillation & aortic, tricuspid & mitral disease.	3	0	52	140	4.8	25.0	106	—	500 mg. every 24 hr.	4
24	M	72	Arteriosclerotic heart disease	7	Not tested	40	144	4.8	23.0	108	—	500 mg. every 24 hr.	4
25	F	64	Arteriosclerotic heart disease	10	0	35	125	4.8	27.0	91	7.43	3 of 500 mg. each	4
26	M	72	Arteriosclerotic heart disease	2½	Not tested	36	143	4.9	32.0	100	—	250-500 mg. every 24 hr.	6

TABLE 1 (*Concluded*).

Case No.	Weight Lost After Treatment lb.	Urine pH After Treatment	Blood Chemical Constituents After Treatment: Nonprotein Nitrogen mg./100 cc.	Sodium millieque./liter	Potassium millieque./liter	Carbon Dioxide millieque./liter	Chloride millieque./liter	pH	Weight Lost* with Last Dose of Mercurial Diuretic lb.	Subsequent Course
1	4	7.5-5.3	24	138	4.0	24.0	103	7.25	Not tested	Patient lost 18 lb. & became edema free with mercurial diuretics & ammonium chloride
2	6	7.3-6.8	92	138	5.0	17.0	110	7.32	10	Patient lost 10 more lb. with mercurial diuretics & became edema free
3	0	7.5-6.5	31	134	3.3	31.0	92	—	3	Patient lost 7 more lb. with mercurial diuretics; discharged improved, but still edematous.
4	6	7.5-5.5	62	134	5.2	22.0	105	—	3	Disease resistant to further therapy with mercurial diuretics
5	3	7.5-6.0	52	132	6.7	23.0	94	7.33	Not tested	Disease resistant to further therapy with mercurial diuretics
6	4	7.7-7.0	34	135	3.6	25.3	102	—	5	Patient lost 5 more lb. with mercurial diuretics but still edematous
7	0	Not tested	38	132	5.2	25.0	97	—	0	Disease resistant to further therapy with mercurial diuretics
8	3	Not tested	98	138	3.8	22.0	107	—	3	Patient discharged without further treatment
9	3	7.0-5.5	78	130	4.3	26.0	101	7.43	0	Disease resistant to further therapy with mercurial diuretics & ammonium chloride
10	1	Not tested	58	135	3.5	42.0	80	—	Not tested	Patient lost 14 lb. & became edema free with mercurial diuretics & ammonium chloride
11	6	7.5-6.5	84	138	4.3	22.0	107	—	0	Disease resistant to further therapy with mercurial diuretics; patient died.
12	11	Not tested	—	—	—	22.5	108	—	2	Patient edema free; no further therapy needed
13	0	Not tested	52	136	3.9	22.4	104	—	0	Patient lost 5 lb. with mercurial diuretics, intravenous injection of aminophylline & ammonium chloride
14	0	Not tested	70	—	—	24.0	102	—	6	Patient discharged still edematous, without further treatment
15	1	Not tested	—	132	4.2	26.0	97	—	0	Patient subsequently lost 6 lb. with mercurial diuretics
16	6	8.3-6.0	—	144	4.9	28.0	105	—	1	Patient discharged without further treatment
17	6	6.5-6.9	—	138	4.7	27.0	99	7.38	6	No further treatment on this admission
	1	Not tested	—	—	—	23.0	—	—	2	Patient lost 22 more lb. with mercurial diuretics & ammonium chloride
18	0	7.4-6.6	55	133	4.5	25.0	96	7.27	1	Patient lost 16 more lb. with mercurial diuretics & ammonium chloride
19	0	Not tested	—	139	3.8	24.0	103	7.30	2	Patient lost 2 more lb. with mercurial diuretics, ammonium chloride & disease then became resistant
20	5	Not tested	32	143	4.6	26.0	107	—	4	Patient lost 3 more lb. without further treatment & then was edema free
21	2	5.1-7.1	72	135	3.6	27.0	99	—	2	Patient lost 15 more lb. with mercurial diuretics & ammonium chloride
	0	Not tested	120	128	6.4	22.0	89	—	Not tested	Patient lost 14 lb. with mercurial diuretics & intravenous injection of aminophylline
22	0	7.5-6.5	—	129	—	25.0	91	7.48	0	Patient lost 20 lb. with mercurial diuretics & ammonium chloride
23	0	Not tested	46	138	4.6	23.5	107	—	Not tested	No response to mercurial diuretics, ammonium chloride and intravenous injection of aminophylline; patient subsequently lost 35 lb. with Southey tubes & paracentesis.
24	0	5.5-6.0	40	141	4.7	26.0	110	—	0	Patient lost 12 lb. with mercurial diuretics combined with ammonium chloride & intravenous injection of aminophylline
25	5	5.5-8.2	—	125	3.8	27.0	94	7.38	4	Patient lost 30 lb. with ammonium chloride, mercurial diuretics & aminophylline
26	2	Not tested	—	148	4.7	28.0	104	—	0	Patient lost 21 lb. with mercurial diuretics combined with ammonium chloride & intravenous injection of aminophylline

*Refers only to weight lost with 1st injection immediately at end of treatment with Diamox.

whereas this degree of response was elicited in 7 of 15 courses in nonazotemic patients. The mechanisms responsible for this relation are not clear. One possibility is that carbonic anhydrase is less important for the over-all reabsorption of bicarbonate when the glomerular filtration rate is low and the filtration of bicarbonate is reduced. It is also possible that azotemia is simply a reflection of the severity of the circulatory insufficiency and therefore of the intensity of the factors operating to retain sodium. Whatever

TABLE 2. *Diuretic Response to Diamox in 26 Patients Given 28 Courses of Therapy.*

WEIGHT LOSS	NO. OF CASES	
lb.		
11	1	(4%)
4–6	9	(32%)
2–3	5	(18%)
0–1	13	(46%)
Total	28	

the explanation, it cannot be said that nonazotemic patients respond well to Diamox since only 1 of these patients lost more than 6 pounds and half lost little or no weight.

The results with Diamox in this study were apparently no more satisfactory than those reported by Schwartz[5] in a smaller group of patients treated with sulfanilamide in doses of 3 to 6 gm. a day. This emphasizes the fact that a carbonic anhydrase inhibitor of greater potency will not necessarily be a more effective diuretic than sulfanilamide, since the factors limiting diuresis with all such compounds are the same.[1] However, increased potency permits employment of smaller doses and thereby probably reduces the incidence of toxic side reactions.

It is of interest that the 2 sulfanilamide-treated patients with the largest diureses (weight loss of 10 pounds) lost large amounts of chloride during therapy.[6] As previously demonstrated[1] effective diuresis with a carbonic anhydrase inhibitor requires chloride loss. The greater responsiveness of these 2 patients was probably due to the fact that they had less severe congestive heart failure, as indicated by relatively large control sodium excretions.[6] In patients with mild degrees of failure Diamox therapy at appropriate intervals may prove to be of value.[3,7]

The meager results obtained in this group of patients contrast sharply with the effects in patients with congestive heart failure due to chronic cor pulmonale. In a significant number of such cases treatment with Diamox appeared to effect large diureses and significant clinical improvement. These data are discussed in another report.[2]

SUMMARY

Twenty-six hospitalized patients with severe chronic congestive heart failure were studied during 28 trials of treatment with Diamox, a new potent carbonic anhydrase inhibitor. Half the group failed to lose weight, and the remainder, with 1 exception, lost only 2 to 6 pounds over an average period of seven days. One patient lost 11 pounds in nine days and became edema free.

Administration of the drug once daily had approximately the same diuretic effect as more frequent dosage, and did not appear to prevent the usual development of mild acidosis and resistance to further therapy. The least favorable response was observed in patients with azotemia. Many patients who had lost little or no weight with Diamox subsequently responded satisfactorily to combined therapy with mercurial diuretics, aminophylline and ammonium chloride.

Diamox administered orally to hospitalized patients with severe congestive heart failure was of little or no clinical value as a diuretic.

We are indebted to Drs. Bernard Jacobson, Dera Kinsey, Samuel A. Levine, Paul D. White and Conger Williams, who permitted the study of their private patients, and to Drs. Maurice B. Strauss and Thomas A. Warthin, who were most helpful in facilitating the study of patients on their services at the Boston Veterans Administration Hospital.

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EOSINOPHILIC GRANULOMA OF THE LUNG*

WILLIAM F. MAZZITELLO, M.D.†

ST. PAUL, MINNESOTA

EOSINOPHILIC granuloma of the lung without associated skeletal or visceral lesions was first described by Farinacci et al.[1,2] in 1951. They reported these cases from an Army general hospital in 2 enlisted men, both of whom had complaints of chronic cough, weight loss, exertional dyspnea and chest discomfort. One patient was thirty-two, and the other twenty-four years of age. The diagnosis was made by thoracotomy and lung biopsy. The histologic appearance of the excised nodules had features identical with that of eosinophilic granuloma of bone. The

*From the departments of medicine, Minneapolis Veterans Administration Hospital and University of Minnesota Medical School.

†Instructor, Department of Internal Medicine, University of Minnesota Medical School; staff physician, Ancker Hospital.

following 2 similar cases were also proved by thoracotomy and lung biopsy.

Case Reports

Case 1. B.R., a 35-year-old oil-burner installer, was admitted to the hospital for the first time on December 15,

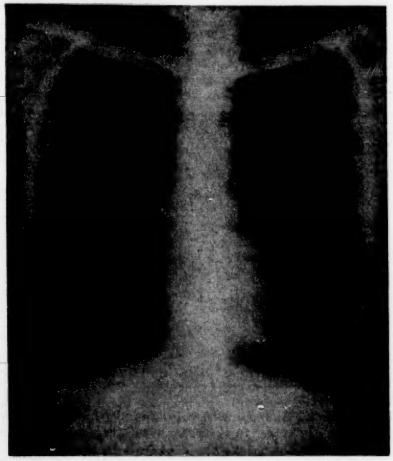

Figure 1. *Posteroanterior Film of the Chest Taken Shortly after Admission in Case 1, Showing Bilateral, Diffuse Nodularity of the Pulmonary Parenchyma.*

1952, with complaints of cough for 2 months, raising of a grayish-white mucopurulent sputum for 2 weeks and then

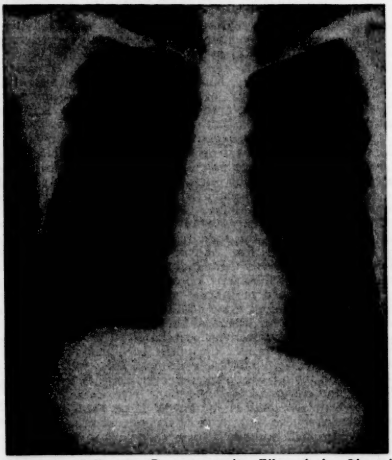

Figure 2. *Follow-up Posteroanterior Film of the Chest in Case 1, Showing Clearing of the Lung Fields Bilaterally.*

foamy white sputum, exertional dyspnea and a weight loss of 13 pounds. In another hospital shortly after the onset of symptoms tuberculin tests were negative, a coccidioidin skin test was +, and x-ray examination of the chest showed diffuse bilateral nodular infiltration. Chlortetracycline and penicillin produced no significant clinical response. The past history revealed otitis media and malaria in 1943, with only 1 recurrent attack of slight intensity in 1947.

Physical examination disclosed a thin, well developed man who appeared chronically ill. There was an old perforation of the posteroinferior quadrant of the right tympanic membrane. A few inspiratory moist rales were noted in the right apical region posteriorly as well as at both bases posteriorly. The remainder of the physical examination was

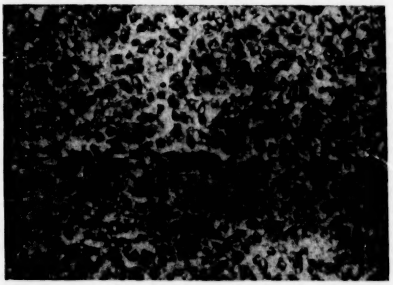

Figure 3. *Photomicrograph of Wedge-Biopsy Specimen in Case 1 (X 150).*

A sheet-like aggregation of cells is seen, showing prominent cytoplasmic vacualization. The dark nuclear aggregates are eosinophilic leukocytes, the granules of which are not demonstrated.

negative. Bronchoscopic examination demonstrated a diffuse erythema of the bronchial mucosa.

The blood pressure was 130/84. The pulse was 96 and regular.

Examination of the blood showed a hemoglobin of 13.5 gm. per 100 cc. and a white-cell count of 14,700, with 87 per cent neutrophils, 11 per cent lymphocytes, 1 per cent basophils and 1 per cent eosinophils. The sedimentation rate was 49 mm. per hour.

Sputum culture revealed *Proteus vulgaris* and diphtheroids. Repeated cultures of sputum and bronchial aspirations

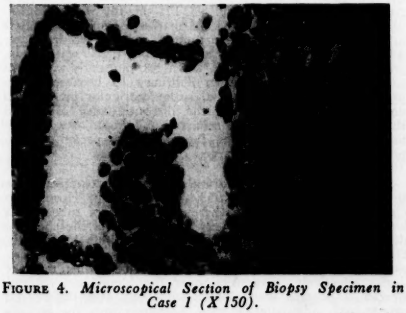

Figure 4. *Microscopical Section of Biopsy Specimen in Case 1 (X 150).*

Syncytium of histiocytes is seen on the left obliterating normal alveolar landmarks; on the right part of an alveolar wall is visualized, showing marked proliferation of the septate cells (mesenchymal elements).

were negative for acid-fast bacilli and fungi. Bone-marrow smears demonstrated myeloid hyperplasia. Bone-marrow culture for fungi was negative, as were P.P.D. (purified protein derivative) in 1st and 2d strength and a histoplasmin

skin test in 1:1000 dilution. A coccidioidin skin test was +. Repeated sputum examinations were negative for asbestos fibers, and bronchial aspirations and sputum for tumor cells. Stools were negative for ova and parasites. The carbon dioxide was 30.2 milliequiv., and the serum potassium 4.9 milliequiv. per liter. The fasting blood sugar was 78 mg. per 100 cc. The prothrombin time was 100 per cent. A bromsulfalein test and a blood Kahn test were negative. Urinalysis was also negative.

Pulmonary-function studies showed an arterial blood pH of 7.41, carbon dioxide content of 22.26 milliequiv. per liter, oxygen saturation of 98.94 per cent, 1st-second vital capacity of 3150 cc. (total, 3700 cc.), maximum breathing capacity of 98,814 cc. per minute, or 58.47 liters per square meter of body surface (normal 61 ± 6 liters), total lung volume of 6863 cc. and residual volume of 2913 cc., or 42.4 per cent of the total volume, and alveolar nitrogen of 1.60 per cent.

X-ray examination of the chest revealed a diffuse increase in the density of both lung fields with numerous areas of nodular density throughout (Fig. 1 and 2). A gastrointestinal series, intravenous pyelograms and complete bone survey were normal.

On January 1, 1953, exploratory thoracotomy showed diffuse nodular disease in all lobes of the right lung, the nodules varying in size from 1 mm. to 1 cm. in diameter. Two wedge biopsies were performed.

Gross examination of the specimen demonstrated small discrete nodules measuring 4 to 10 mm. On section of the nodules peculiar firm, mottled-gray and black granular areas were noted.

On microscopical examination (Fig. 3 and 4) the centers of the nodules were made up of moderately large cells with oval nuclei that had a fine chromatin pattern, 1 or 2 nucleoli and a moderate amount of pale, eosinophilic cytoplasm. The cell boundaries could not be made out easily, and the tissue had the appearance of reticulum. These were surrounded by a zone of lymphocytes and macrophages, and the surrounding lung tissue disclosed some thickening of the alveolar septums by lymphocytes and macrophages in the immediate vicinity of the nodule. In addition many eosinophils were sprinkled through the nodules. There was no necrosis and no organisms or foreign body. Some of the arteries in the immediate vicinity of these nodules revealed hyaline thickening of the wall and a low-grade inflammation.

Both before and after operation the patient experienced minimal to moderate chest discomfort. However, he was soon ambulatory, with relatively mild exertional dyspnea that lessened during the remaining period of hospitalization. From February 3 ACTH, 50 units, was given daily in 2 divided doses for 3 days, when administration of 40 units of ACTH gel was begun daily. ACTH therapy was discontinued on February 10 because of marked generalized muscle aching, drowsiness, malaise and tachycardia. Two days later administration of 200 mg. of cortisone daily was begun, continuing until February 17, when 100 mg. daily was given until it was discontinued on February 19 because of repeated episodes of paroxysmal supraventricular tachycardia and precordial pain. After the discontinuance of steroid therapy no similar episodes occurred. The patient was practically asymptomatic during the remaining period of hospitalization and was discharged on April 16.

CASE 2. D.M., a 23-year-old soldier, was transferred to the hospital on April 17, 1953, from the Army Hospital at Camp Carson, Colorado, where a diagnosis of tuberculosis had been made. Routine x-ray examination of the chest on discharge had revealed diffuse densities in both lung fields. He had had a chronic cough for 7 months. He had been asymptomatic otherwise and had carried out his military duties effectively. Examination of the blood had demonstrated a normal hemoglobin, white-cell and differential counts and sedimentation rate. Serologic tests for syphilis were negative, as were smears and culture of sputum and bronchial washings. Skin tests for histoplasmosis and coccidioidin and 1st-strength and 2d-strength P.P.D. were also negative; dilution to 2½ revealed + induration at the end of 72 hours. On this basis and the x-ray evidence of lesions of the chest, the patient was given antituberculosis drugs, receiving a course of streptomycin and isoniazid. No changes were noted after 2 weeks of this therapy.

On admission he was afebrile and complained only of a slight persistent cough. Physical examination was negative. The blood pressure was 130/65. The pulse was 80 and regular.

Blood chemical constituents were as follows: potassium 4.3 milliequiv., sodium 145 milliequiv., chloride 104.3 milliequiv., and carbon dioxide 30.6 milliequiv. per liter. The calcium was 10.1 mg. and the inorganic phosphorus 3.8 mg. per 100 cc. The total protein was 7.4 gm. per 100 cc., with an albumin of 5.0 and a globulin of 2.4 gm. The blood urea nitrogen was 10 mg. per 100 cc. Total cholesterol was 189 mg. and cholesterol esters 144 mg. per 100 cc. (76.2 per cent). The prothrombin was 67 per cent. Cephalin cholesterol flocculation was normal; urinalysis was negative, and urea clearance normal. The blood Kahn test was negative.

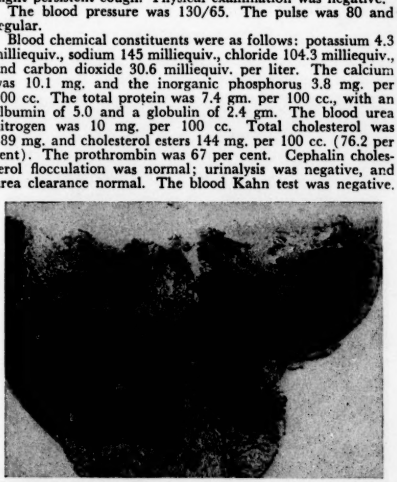

FIGURE 5. *Wedge-Biopsy Specimen of the Right Lung in Case 2, Showing Subpleural Localization of Granuloma, with Evidence of Compression Atelectasis and Emphysema of the Contiguous Pulmonary Tissue (X 1.8).*

Examination of the stools showed no ova or parasites. Sputum stained for eosinophils was negative, as were tuberculin tests with P.P.D. in 1st and 2d strength.

Histoplasmin and coccidioidin skin tests were negative. X-ray study of the chest demonstrated widely disseminated fibronodular infiltrate in both upper lobes, with some extension into the lower lobes. Numerous areas of rarefaction were seen, probably representing multiple small cavities. Planigrams revealed no mediastinal abnormality or disease of the bronchial tree. X-ray films of the hands, pelvis, lumbar and thoracic spine and skull were normal. A supraclavicular fat-pad biopsy, bone-marrow biopsy and bronchoscopic examinations were negative. Bronchial washings were negative for tumor cells, and smear and culture for acid-fast bacilli and fungi.

On the basis of this negative diagnostic work-up an exploratory thoracotomy was performed. Diffuse nodularity of the entire right lung was noted, with a few fine apical pleural adhesions. Wedge biopsies were taken from the lateral aspect of the upper lobe and from the medial inferior portion of the right lower lobe.

The specimen consisted of a wedge resection from the posterior segment of the right upper lobe measuring 4 by 2 by 2 cm. Numerous firm, tan nodules, 1.5 cm. in greatest diameter, were present throughout the specimen. Approximately 10 such nodules were observed; they were confluent, with vaguely defined peripheral edges. There was definitely no fibrous wall around these nodules, and no actual caseous material was present. Some of the nodules appeared to retain some of the parenchymal markings. The nodules were so numerous as to render the entire specimen firm to palpation. There were no larger bronchi that could be dissected. The pleura was puckered over some of the nodules (Fig. 5) and elevated in a dome shape over others.

Microscopical examination showed large areas of pulmonary parenchyma to be replaced by a mass of cells composed of reticulum cells and small foam cells with a sprinkling of lymphocytes at the extreme periphery. Near the centers of the nodules large numbers of eosinophils were found in greatest concentration, although they were actually scattered throughout the nodule itself. No organisms or parasites could be found, and no caseation was present. The appear-

ance of the lesion was identical with that of an eosinophilic granuloma of the type that is often seen in bone.

The postoperative course was uneventful, with only slight discomfort at the operative site. This decreased progressively.

Intramuscular injection of ACTH gel was started on June 8 in a dosage of 10 units daily and continued to June 16, when 20 units was given daily for 6 days. Then the dosage was increased to 40 units daily and continued for 12 days until July 3. No reactions were noted at any time and the patient had a definite sense of well-being while on the drug. He was asymptomatic at the time of this report.

Review of the Literature

The term "eosinophilic granuloma" was first applied in 1940 by Lichtenstein and Jaffe[3] to a new and previously unrecognized lesion of the bone in a four-year-old child. In this case and in others[4] the lesions were solitary, started in the medullary cavity and tended to erode, expand and perforate the cortex with replacement of bone by a soft, yellow or brown tissue; histologically, the lesions were characterized by conspicuous sheetlike collections of histiocytes and the presence of numerous eosinophilic polymorphonuclear cells. In addition there were hemorrhage, necrosis and varying numbers of multinuclear giant cells, some of which showed phagocytic activity. Although the authors recognized the basic cell involved as a histiocyte they gave the name "eosinophilic granuloma of bone" to these lesions because of the prominent eosinophilic cellular infiltration.

Further review of the literature discloses that Finzi,[5] in 1929, described "a myeloma with a preponderance of eosinophilic cells" in a circumscribed lesion of the frontal bone in a fifteen-year-old boy. Also, in 1935, Fraser[6] observed skeletal lesions similar to those reported by Lichtenstein and Jaffe, and called them skeletal lipoid granulomatosis. He described the pathologic changes as occurring in three stages: endothelial-cell proliferation, eosinophilic-cell infiltration and lipoid storage.

On the basis of gross and microscopical studies of pathological material obtained from their patients Farber[7] and Green and Farber[8] differed with Jaffe and Lichtenstein, believing that these benign destructive lesions of bone did not constitute a new process but were a variant of a basic pathologic pattern known as Hand–Schüller–Christian disease and Letterer–Siwe disease. They found many grades of transition from Hand–Schüller–Christian and Letterer–Siwe disease to eosinophilic granuloma.

Mallory[9] agreed with this concept of a single entity. He defined Letterer–Siwe disease as one with a rapidly fatal course, the patients seldom living beyond two years of age. It is characterized clinically by fever, skin rash, rapidly progressive anemia and purpura, with histologic evidence of marked proliferation of the reticuloendothelial cells in all parts of the body, especially the skin, lymph nodes, spleen and liver, and with occasional focal bone involvement. After the age of two the course is chronic and manifested by histologic changes of Hand–Schüller–Christian disease. This is generally considered to constitute the intermediate stage, histologic features of both Letterer–Siwe disease and eosinophilic granuloma occasionally being present at the same time.

Lichtenstein and Jaffe[3] believed that cases of Hand–Schüller–Christian disease should show collagenized and lipidized lesions classified as lipogranuloma, protracted course of illness over a period of ten to fifteen years, stunted growth and the characteristic triad. However, the complete triad is not necessary for the diagnosis. The final stage is eosinophilic granuloma, occurring in adolescence and adulthood and running a benign course.

Henderson et al.[10] did not agree that the three phases could be differentiated solely by histologic means. They showed that the histologic classification alone was at definite variance with the accepted clinical picture. They believed that both must be evaluated jointly for correct final diagnosis. In their series the average age incidence for eosinophilic granuloma and Hand–Schüller–Christian disease was seventeen and nineteen years.

Schuknecht and Perlman[11] stated that eosinophilic granuloma was a bone lesion per se and that if visceral lesions were present at the same time, a diagnosis of Hand–Schüller–Christian disease should be made.

Hodgson, Kennedy and Camp[12] reviewed the roentgenologic aspects of 28 cases of reticuloendotheliosis, under which they grouped Letterer–Siwe disease, Hand–Schüller–Christian disease and eosinophilic granuloma. They found that the skull was most frequently involved, the pelvis, femur, ribs, humerus and scapula following in that order. No roentgenologic differentiation was possible, except with added clinical history. These authors further claimed that as a general rule pulmonary involvement was absent, unless skeletal lesions were also present.

However, only a few cases of pulmonary involvement in the so-called xanthomatous diseases have been reported in the literature to date, and these have always been associated with skeletal and visceral lesions.

Rowland,[13] in 1929, described a case of xanthomatous eosinophilic granuloma of bone in association with diffuse pulmonary lesions, which at autopsy were found to be communicating vesicular cavities, varying from the size of a pinhead to that of a pea.

In 1943 Currans and Popp[14] cited the case of a twenty-nine-year-old woman who presented multiple skeletal defects and bilateral pulmonary fibrosis. Definite clearing of the pulmonary lesion followed x-ray therapy.

In 1947 Weinstein et al.[15] reported the case of a thirty-one-year-old man with multiple skeletal lesions of cosinophilic granuloma accompanied by diffuse bilateral nodular infiltrations of the lung fields. X-ray therapy produced satisfactory regression of both the skeletal and the pulmonary lesions. A year later Schuknecht and Perlman[11] presented a case of a thirty-

year-old man with multiple skeletal lesions and diffuse soft infiltrative lesions in the lung fields bilaterally extending out from the hilar regions. In 1949 Parkinson[16] reported the case of a fifty-six-year-old man who had skeletal and clinical manifestations of a transition between eosinophilic granuloma of bone and Hand–Schüller–Christian disease with pulmonary infiltration and polycystic or "honeycomb lungs." Oswald and Parkinson[17] described this type of pulmonary lesion as a variety of cystic disease in which thin-walled cysts were distributed uniformly throughout the substance of both lungs, varying in size up to 1 cm. in diameter. Histologic examination revealed diffuse fibrosis and lipoid cell proliferation in the interstitial tissue. The authors believed that these changes were associated with the xanthomatous diseases. Lackey, Leaver and Farinacci,[2] in 1952, reported the case of a nineteen-year-old soldier who was found to have multiple skeletal lesions diagnosed by biopsy as eosinophilic granuloma, in conjunction with x-ray evidence of diffuse nodular infiltrates in both lung fields. These lesions were similar roentgenologically to their 2 cases of isolated pulmonary granulomas.

In a review of the entire subject Lichtenstein[18] recently stressed the previously mentioned concept in which these diseases are represented as variants of a single pathologic entity of unknown etiology. He further discussed the confusion in terminology and proposed a new term, "histiocytosis X," as an all-inclusive name, with eosinophilic granuloma as a localized form, and Letterer–Siwe's syndrome and Hand–Schüller–Christian's syndrome as disseminated forms. The term "histiocytosis" refers to the essential type of histologic cellular reaction occurring in these diseases, and "X" indicates the need for the identification of an etiologic agent. Lichtenstein further pointed out that the segregation of these entities into certain age groups is incorrect, for Letterer–Siwe disease may occur in adults as such or as a terminal acute phase of long-standing Hand–Schüller–Christian disease. He also called attention to the probability that eosinophilic granuloma occurred in different viscera of the body as well as in skeletal sites.

His interpretation was that isolated pulmonary lesions of eosinophilic granuloma are accompanied by visceral lesions undetected at the time or manifested in the ensuing months or years. The possibility that such undetectable visceral lesions were present in the 2 cases reported above cannot be denied, and a follow-up period of observation will be necessary for proper evaluation. However, it might also be postulated that eosinophilic granuloma of the lung may be present as a primary entity, without associated skeletal or other visceral disease, just as eosinophilic granuloma of bone may occur as a single lesion.

It is also interesting that Lichtenstein emphasizes the little known pulmonary interstitial fibrosis and so-called "honeycomb disease of the lungs," which may be frequently associated with or residua of these states. It is believed that in the future "honeycomb disease of the lungs," as described by Oswald and Parkinson,[17] will become more definitely recognized as being the pulmonary-tissue corollary to the sclerosing fibrous-tissue reaction in healed skeletal lesions of eosinophilic granuloma.

Therapy

The treatment of associated pulmonary lesions in proved eosinophilic granuloma of bone and Hand–Schüller–Christian disease has been mentioned by different investigators. Currans and Popp,[14] in 1943, reported a case in which multiple skeletal defects were associated with diffuse bilateral pulmonary fibrosis that showed minimal clearing after x-ray therapy. In 1947 Weinstein et al.[15] described combined skeletal and pulmonary lesions, which cleared satisfactorily with x-ray therapy. In 1938 Dickson[19] reported the case of a thirty-year-old man with multiple skeletal lesions proved by biopsy to be eosinophilic granuloma as well as diffuse infiltration of the lung fields bilaterally; x-ray therapy of the pulmonary lesions resulted in no discernible improvement.

In the case presented by Lackey et al.[2] multiple skeletal lesions of eosinophilic granuloma, with x-ray evidence of a diffuse granulomatous nodular pulmonary infiltrate throughout both lung fields, received multiple courses of x-ray therapy; no change was observed in the pulmonary lesions but satisfactory improvement in the skeletal lesions occurred.

Brody and Gilliespie[20] reported the administration of ACTH to a twenty-four-year-old soldier who had multiple skeletal lesions of eosinophilic granuloma, proved by biopsy, and x-ray evidence of diffuse fine mottled infiltrations throughout both lungs; 50 mg. of ACTH was given intramuscularly every six hours during the first day, and on the second day, after the patient had received a total of 300 mg., an ache in the lower back, muscular pains in both legs and a moderate amount of spasm in the lumbar muscles developed. The dose was then decreased to 25 mg. every six hours, and because of the extreme pain and daily fever, the drug was discontinued after a total of 600 mg. had been given. No improvement was noted. The subjective discomfort on ACTH therapy was similar to the reaction experienced in Case 1 reported above.

In 1 of the 2 cases with lesions limited to the lungs reported by Lackey et al.[2] 800 mg. of ACTH and 5700 mg. of cortisone were given. There was definite evidence of clearing six months after admission to the hospital, but some nodular infiltrate persisted at the time of the report.

In Case 1, reported above, 310 mg. of ACTH and 1200 mg. of cortisone were given before marked subjective discomfort necessitated the discontinuance of this therapy. No other treatment was given, and at time of discharge moderate clearing was noted. However, Case 2 received 555 units of ACTH, and a sense

of well-being was evident, with some clearing of the pulmonary fields.

From these observations it is evident that the treatment of the pulmonary lesions is still undecided. Many more cases will have to be evaluated to determine accurately the effectiveness of ACTH, cortisone and x-ray therapy in this disease.

Discussion

The occurrence of eosinophilic granuloma as a primary pulmonary condition without associated skeletal and visceral lesions is considered to represent another variety of this disease. Solitary pulmonary lesions could well be compared to solitary skeletal lesions, and the benign clinical course observed in the cases described above and in those reported by Farinacci et al.[1] is also compatible. Thus, only a new primary site for the occurrence of a well known disease is manifested and not a new pathologic entity per se. The reactivity of the involved tissues, regardless of site, indicates a definite response by and involvement of the reticuloendothelial system. Whether cellular lipoid disturbance is primary in eliciting this tissue reaction or merely the secondary components of an unknown primary etiologic agent has yet to be elucidated.

The pulmonary lesions reported in these cases have a remarkable individuality and are still similar enough to other pulmonary diseases to necessitate a thorough differentiation by clinical and laboratory studies. Thus, tuberculosis, sarcoidosis, Loeffler's syndrome, asbestosis, adenomatosis, malignant lymphoma, berylliosis, histoplasmosis, coccidioidomycosis and "cave disease" would have to be considered in the differential diagnosis. The presence of eosinophilic leukocytes in the lesions of eosinophilic granuloma and Loeffler's syndrome necessitates closer attention to the differentiation of these two diseases. This is readily accomplished when one remembers that by definition Loeffler's syndrome consists of transient pulmonary lesions that vary in location from one day to the next and usually disappear completely within two weeks of the onset. Also, eosinophilia is a constant feature. These characteristics are in decided contrast to the clinical and laboratory findings in the cases reported above and those described by Lackey et al.[2]

Finally, the eventual presence or absence of secondary pulmonary-tissue changes occasioned by these granulomas must be considered. Lichtenstein[18] mentions the possible progression of the pulmonary lesions into a diffuse interstitial fibrosis, with subsequent production of the clinical picture of chronic cor pulmonale. In Case 1 pulmonary function was studied, and no significant variances from normal values were encountered. It is realized that these investigations were done when the pulmonary lesions were of the granulomatous type; only repeated studies of pulmonary function at long intervals will demonstrate whether or not the disease will ultimately progress into the stage of chronic interstitial fibrosis with subsequent impairment of ventilatory function of the lungs.

Summary

Two new cases of eosinophilic granuloma of the lung are reported. The similarity of these pulmonary lesions to the isolated skeletal lesions of eosinophilic granuloma as primary manifestations of the disease is pointed out, and a similar chronic benign clinical course is expected.

A review of the literature is presented, and the relation of Letterer–Siwe's disease, Hand–Schüller–Christian disease and eosinophilic granuloma as variants of a single entity is discussed.

ACTH, cortisone and x-ray treatment of the pulmonary lesions are considered.

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COMPLICATIONS OF ANTICOAGULANT THERAPY

Review of the Literature and Report of a Case

CAPTAIN ROBERT C. RAINIE, USAF*

DURING the past decade there have been many studies on thromboembolic disease. Most authors agree that anticoagulant drugs are an important addition to the armamentarium. It is unfortunate that with the use of most new drugs, undesirable features appear that cannot be overlooked. The anticoagulants are no exception. The only known complication is hemorrhage, but there are numerous contraindications: blood dyscrasias manifesting hemorrhagic tendencies; large open surfaces with poorly controlled hemostasis after operation (especially liver and prostatic surgery); brain and spinal-cord surgery; active or imminent gastrointestinal ulceration or bleeding; malignant hypertension,[1] particularly when there has been a previous cerebral hemorrhage; and subacute bacterial endocarditis. The most important contraindication—the lack of adequate laboratory facilities—if combined with an inexperienced physician may have disastrous results. Heparin should be avoided in patients with renal disease, but it has recently been shown[2] that Dicumarol may be used safely if carefully supervised. Although anticoagulants have proved of definite value in reducing the incidence of thromboembolism in congestive heart failure[3] they must be administered cautiously in the presence of hepatic insufficiency.[4]

The incompatibility of lumbar sympathetic blocks and other deep needle-puncture procedures and anticoagulant therapy has been stressed in several reports.[5-8] Lilly and Lee[7] described 4 autopsied cases of fatal Dicumarol poisoning, all of which showed profuse retroperitoneal hemorrhage at the sites of lumbar sympathetic blocks. One of these disclosed a hemorrhage into the spinal cord as a result of a diagnostic lumbar puncture. Another patient with a fractured hip was given anticoagulants two weeks after operation, with resultant extensive ecchymosis at the site of the pinning. Fatal bleeding may occur even while the induced hypoprothrombinemia is within the therapeutic range, as demonstrated by O'Connor et al.[8] It is their opinion that all deep needle-puncture procedures are probably contraindicated during Dicumarol therapy, they are better done three or four hours after the last previous dose of intermittent heparin therapy. Pratt,[9] however, believes that sympathetic blocks and anticoagulant therapy complement each other and, if done with caution and skill, may be used to the benefit of the patient. I prefer to use deep needle puncture only when no bleeding tendency exists.

*Ward officer, 3630th USAF Hospital, Sampson Air Force Base, New York.

The risk of properly supervised anticoagulant therapy in myocardial infarction is relatively minor. Experimentally, surface hemorrhages were found to be no commoner in anticoagulant-treated myocardial infarction than in controls.[10] Although Russek and Zohman,[11] in a questionnaire study on this problem, reported a much higher incidence of serious hemorrhage, this finding must be further supported before current views and practices are abandoned.[12] In the meantime reports of hemorrhagic complications that may or may not have been due to the use of anticoagulants continue to appear.[13]

There is little doubt that the production of hemorrhagic sweet-clover disease of animals in man is a reflection not on Dicumarol but on the method of its use. Shlevin and Lederer[14] tried unsuccessfully to correct the hemorrhagic diathesis caused in a patient who received twenty-one days of uncontrolled Dicumarol therapy. The futility of their attempts was further emphasized by the autopsy finding of hepatic cirrhosis, a contraindication to even the consideration of Dicumarol therapy. Another patient, described by Duff and Shull,[15] received Dicumarol for thirty-seven days without prothrombin determinations; hemoptysis, hematuria, oral and vaginal bleeding developed, and autopsy disclosed cerebral, subarachnoid, cardiac, renal, hepatic, pulmonary, periosteal, retroperitoneal and cutaneous hemorrhages.

In a report of 4 cases and review of 32 deaths attributed to Dicumarol poisoning Wright and Rothman[16] were much less confident of the beneficial effects of Dicumarol. There was a definite lack of correlation between the prothrombin percentage and the bleeding tendency. Of their 4 patients 2 died from gastrointestinal hemorrhage, 1 from pulmonary hemorrhage, and 1 from cerebral hemorrhage, and in each the prothrombin percentage was in or above the accepted therapeutic range. Contrariwise, a twenty-two-year-old patient with poliomyelitis received, through error, 300 mg. of Dicumarol for four consecutive days, resulting in a toxic hypoprothrombinemia, and yet this patient, even though subjected to a lumbar puncture, gave no evidence of even minor hemorrhage. Such cases as these are difficult to reconcile, and further demonstrate that factors besides the prothrombin percentage must be involved in these undesirable and unpredictable hemorrhagic complications.

In 1947 and 1948 numerous publications from the Mayo Clinic[17-20] indicated that in general one might expect minor bleeding in about 4 per cent and serious bleeding in about 2 per cent of patients receiving anticoagulants. There was only 1 case of untoward

bleeding, uncomplicated hemarthrosis, in an early group of 50 patients with myocardial infarction treated with anticoagulants.[20]

It is evident from the questionnaire data obtained by Nichol[21] in 1950 that there are many unreported cases of hemorrhagic complications occurring during the use of anticoagulants. In his replies from 136 physicians there was a 2 per cent incidence of major hemorrhage in 15,500 patients.

More recently Urdan and Wagner[22] reported a survey of 450 gynecologic patients who were treated with Dicumarol after operation and experienced no serious bleeding. There were 4 cases of epistaxis, ecchymosis and hematuria requiring no special therapy in a group of 189 anticoagulant-treated cases of myocardial infarction.[23] A 10 per cent incidence of hemorrhagic complications in 100 cases of postoperative Dicumarol therapy was reported in the foreign literature by Fayre-Gilly et al.[24] Of these side effects only 2 per cent were severe, 1 being a fatal retroperitoneal hemorrhage.

Although heparin is considered the least dangerous anticoagulant because of its abbreviated period of activity, phenylindanedione has been used in at least 417 patients[25,26] without evidence of serious bleeding. This indicates that, properly used, this drug has a low incidence of toxic side effects.

Flaxman,[27] in 1950, reviewed 107 cases of fatal drug poisoning over a five-year period and made the disturbing discovery that Dicumarol was the most common cause of deaths resulting from drugs given orally. This placed more emphasis on the data stressed in an editorial[28] in the same year that summarized the hemorrhagic hazards of the anticoagulants and again gave to the physician the responsibility of assuring proper dosage of drug, accurate laboratory studies and prevention of ill advised surgical procedures.

It is with this review in mind that the following case is presented.

Case Report

C. W. (No. 47129), a 19-year-old airman, was admitted to the hospital on May 25, 1953, with a chief complaint of pain in the right leg. He had been in good health and had spent the previous afternoon on a strenuous bivouac. As he got off the bus at mess hall he felt a severe pain in the calf of the right leg—like that of a pulled muscle. On the following day he reported to the hospital, where the right calf was found to be swollen, tender and warm. There was no erythema, dilated superficial venous pattern or cyanosis. Homans's sign was positive. A diagnosis of venous thrombosis secondary to excessive effort was made.

The past and family histories were noncontributory, and laboratory studies were within normal limits.

He was placed on bed rest, with hot, moist compresses applied to the elevated leg, and given penicillin, 600,000 units every 12 hours. Heparin was administered intravenously for 2 days. The prothrombin percentage activity was within the normal range (Fig. 1). On May 27 the patient was given 200 mg. of Dicumarol, and this was repeated the next day. A urinalysis on May 29 showed microscopical hematuria. Although the prothrombin level was 14 per cent on May 30, 50 mg. of Dicumarol was administered. The prothrombin remained between 12 and 14 per cent, and on May 31 and June 1 profuse epistaxis occurred, requiring cauterization. Another 50 mg. of Dicumarol was given on June 2, and the prothrombin remained at 12 per cent. At no time was the patient given whole blood or vitamin K to correct the hypoprothrombinemia. On June 5 swelling and diffuse ecchymosis of the right leg appeared. He was given no more Dicumarol, and on June 8 the prothrombin was 29 per cent, returning to 84 per cent 8 days later. Microscopical hematuria was noted on June 10. On June 18 examination revealed a tight Achilles tendon on the right and sustained ankle clonus. The Babinski sign was absent, but the Oppenheim sign was positive. A spinal puncture was normal in all respects except for a protein of 100 mg. per 100 cc. Four days later he was seen by a neurologist, who found right-ankle clonus, atrophy of the right gastrocnemius muscle and weakness on dorsiflexions of the right

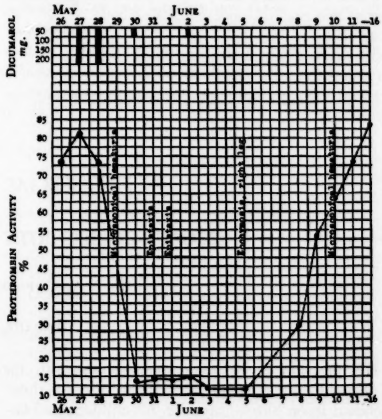

Figure 1. *Effect of Dicumarol Therapy. On June 18 pyramidal signs developed in the right leg with a spinal-fluid protein of 100 mg. per 100 cc.*

foot. His impression was that the patient had probably had a mild intracerebral hemorrhage secondary to anticoagulant therapy. With physiotherapy the spasticity of the right calf gradually improved, with complete clearing of the signs. Laboratory studies gave no evidence of liver disease or blood dyscrasia. At no time was there any acute episode suggesting intracranial bleeding.

Summary

A review of the literature of the past decade concerning the hemorrhagic complications of anticoagulant therapy is presented.

A case of thrombophlebitis demonstrating the potential hazards of these anticoagulant drugs is reported. It is re-emphasized that a reliable laboratory and a competent physician are essential for correct use of these drugs. Direct effects of the anticoagulants on the vascular wall have not been determined, and individual idiosyncrasies cannot be predicted.

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SPECIAL ARTICLE

ECONOMIC SECURITY FOR THE PHYSICIAN*

JOHN ALAN APPLEMAN, A.B., M.A., J.D.†

URBANA, ILLINOIS

THE problem of economic security concerns the physician not only for himself but also for those dependent upon him — his wife, his children and occasionally his grandchildren, parents and other relatives. With certain limitations the analysis of these problems and lending of specialized assistance in their solution falls into the field of estate analysis or estate planning. This requires a knowledge of intricate aspects of the law — primarily in the fields of insurance, probate, wills, trusts, taxation and future interests. Unfortunately, specialists are as yet few, since the busy family attorney, enmeshed in a multitude of diverse phases of the law, does not have the time to concentrate on this field of activity.[1] If the physician desires expert help, he must find an expert, who will save him and his estate substantial fees many times over.‡ Above all, he must avoid reliance upon legal advice offered by laymen who may utilize some learned-sounding language, or purport to render estate planning services, but who may open up a thousand pitfalls for him.

*Adapted from the chapter entitled "Economic Security" in the forthcoming book, *The Physician, His Practice and His Business*, by permission of the publishers, Little, Brown and Company, Boston.

†Member of the bars of Illinois, District of Columbia, Kentucky, United States Supreme Court and Tax Court.

‡Unfortunately, lawyers are not permitted — as physicians are — to list their fields of special study and qualification, nor do bar associations even recognize the existence of specialties, except for patent or copyright law. This attitude has been carried to the point of absurdity by attempts to prohibit life underwriters from telling their clients of attorneys with particular qualifications in the fields of taxation and estate planning. Banks are not a safe source of information, since they tend to recommend their own, or friendly, attorneys, who favor such banks for trust business. It would be well for the physician seeking a specialist to find out what the attorney has written on the subject, the lectures he has given, his training and background and so forth. These are certainly reasonable bases of inquiry, and should not insult any properly qualified person.

PROPER MENTAL APPROACH

When one speaks of economic security it must be remembered that security is itself a relative term. To an intern an earlier graduate's income of $10,000 a year generally seems quite large. Yet a physician who earns $25,000 a year may not feel prosperous; there are too many things competing for slices of his income. Similarly, it is impossible to give all members of one's family perfect financial security either during the physician's lifetime or upon his death. The man who seeks to achieve such an unattainable end by driving himself intolerably hard, becoming a tense and nervous husband or father and breeding ulcers and hypertension in himself or others is unwise. Life is meant to be lived in the present tense, not in retrospect. Yet too few persons realize this fact, and may sacrifice what is worth while in life for this financial will-of-the-wisp.[2]

This is the first point to be considered in undertaking to analyze one's affairs and to chart a path either for a future career or for the years that may remain to a man already well advanced in his professional life. Personal factors may cause an economic shipwreck or keen personal distress. One of these

factors is that, in these days, the physician's income frequently develops too rapidly. Having saved and labored for long years, when other people of comparable ages were beginning to surround themselves with the luxuries of life, he and his wife often think that they have to make up for lost time.

In these days when high income taxes, grocery bills, utilities and other current expenses leave a minimum of capital savings with which to pay for luxury items, it must be understood that certain financial goals are not attainable in a single year or even in five years. It is far better for the physician to persuade his wife to read these pages, to discuss their problems frankly together and to face squarely their social and economic temptations than to plunge into the never-ending effort of keeping up with the Joneses. Many a sound physician has been broken in tranquillity or health from trying to meet this pace. All that is required to combat this urge is patience, an ability to look at one's self honestly and a sense of humor. The first essential, then, is, "Physician, heal thyself" — of untoward social ambition if a tranquil and happy life is desired.

Wisdom of a Conservative Investment Program

Economic security may usually be attained if one acquires, over a period of years, equities of various types that enhance in value. These may develop in part by methods that are not normally recognized as avenues of savings — such as payments for a home or life-insurance premiums. If these average out, over a thirty-year period, together with other savings or investments, at $5000 a year (and in peak years they may be considerably greater) the total accumulation alone will amount to $150,000. Interest earned and enhancing the total — even without rising capital values — would bring it to an amount in excess of $200,000. Therefore, it is clearly not necessary to plunge into risky or untried ventures in an effort to achieve financial security too rapidly. One is more apt to lose the entire capital accumulations by trying to compete in an unfamiliar field. Physicians are notoriously easy marks for fast promoters of every type. Is it not time to reverse this tendency?

General Principles of Investment

The best time to make an investment, as a rule, is when others are following an opposite course. Most people sell stocks or farms in the middle of a depression. That is the best time, of course, to buy — not on the boom markets, when the income, averaged over a twenty-year basis, will not return over 1 or 2 per cent annually on the investment.

It is not possible to find an investment counsel in any area who is expert in all possible methods of investment. The stock broker is no expert in farms or rental real estate. Each of these investment subjects could fill a text. The following few comments may be of help to the physician faced with this problem:

He should try to diversify his holdings to the extent that 25 per cent or better of net worth is in "equity holdings" — such as soundly chosen common stocks.

If he cannot afford a widely diversified stock portfolio he should check over investment-syndicate stocks or mutual fund shares offering this diversification. However, he should study their past records with care and bear in mind that an excellent record for the period from 1940 onward does not mean that a like result would follow if the country entered a new era similar to that from 1929 to 1938. Also, he should buy for the future, preferably in the field of "growth" type of securities, avoiding stock research services in an effort to try to become his own expert. Many brokers have read them for years and are far from financially secure.

If he buys farm land, it should be in his own county or near at home, where he can talk to the tenant over the telephone, watch his performances and replace him if necessary. The best land, not the poorest, should be purchased even though it costs more — but in a period when the price is not three times its average cost over the past twenty years. And the money should not be put back into farmhouses. Such items are nonproductive and expensive. Land with no buildings at all, rented out to an adjacent farmer, is usually the most satisfactory — unless the physician chooses to live on the farm himself.

If he buys rental real estate he should avoid expensive properties — for example, a $30,000 property that brings in $150 a month. Instead, he should buy property that will gross between 15 and 25 per cent a year, and net not less than 10 per cent. It may not give him pride of possession, but is a far better type of investment. And commercial real estate, for many reasons, is generally better than residential real estate.

The physician should select investments that fit his personality. One person will gravitate naturally toward farms; some will shun rental real estate, because of fear of vacancies, plumbing bills and so forth, and others have an aversion to the stock market. Each person should select the type of investment with which he will be content, but should seek to diversify his holdings between dollar and equity types so that he can face the hazards of inflation and deflation with equal equanimity. No estate analyst will give the physician investment advice in any specific detail, because of the wide variation in clients' personalities and variations in opportunities according to localities. Each man must work out for himself the basic approaches to investment that will suit him best and then obtain the advice of several competent and honest persons familiar with investments available within those narrow limits.

A physician should bear in mind even more keenly than a layman the possibility of "little strokes," which may affect his business acumen in later years and cause the dissipation of his funds. It would not be amiss, after the investment program has been well crystallized, — perhaps by the age of fifty, — to shift the assets to a corporate trustee, with reasonable restrictions against one's own improvidence, as much as can be done consistently with prevailing state law. And if he is fearful of his own judgment, or desirous of ridding himself of investment problems, he can shift these duties from their very inception to a corporate trustee. He should understand, however, that such a trustee will generally be ultraconservative, which means that any future enhancement in capital worth will be quite modest.

Creating an Insurance Program

To turn from the ways of enhancing capital to ways to keep from losing it, the quickest methods of loss are doubtless those occurring from casualties and catastrophes. The former are generally regarded as including injuries to the person, and the latter damage to one's property.

No physician is so wealthy that he can afford to carry all the risks of possible loss from his personal funds. Nor would he be wise to do so, even if he could, since he is not an expert in the handling of claims and litigation. So he, and others like him, pool their resources together and hire experts to exercise supervision. This is called insurance.

It is inadvisable for the physician to shop around personally for the numerous coverages that he will require. He is too busy to be bothered with the details; in addition his inexperience will generally produce a superfluous, expensive and yet inadequate program. The best way to put a plan of coverage into operation is to have a reputable and experienced broker handle all these policies, except life insurance, through major companies. Having a single broker at any one time will also avoid the time wasted in listening to competing agents.

It is also recommended that renewals be planned to fall due on a single, or perhaps semiannual, date, such as June 1, or perhaps May 1 and October 1 if two dates are desired, to make it easy to check coverages, even though this produces a good-sized bill that arrives on one or two occasions. It is better not to have this bill fall due at the same time as that of substantial income-tax or real-estate-tax payments. Life insurance should not be handled by this broker, nor should life-insurance premiums necessarily bear the same anniversary date as the other coverages.

The following are some of the coverages to be taken into consideration:

Liability Coverages

Malpractice. Any reputable insurer is satisfactory, but the largest limits one can obtain should be purchased. Anyone can err, and today's juries place no limit on damage verdicts.

Owner's, landlord's and tenant's liability insurance. This protects the insured, whether he is the owner or the tenant, against suits brought as a result of falls due to the neglect of a nurse or other employee, the too-slick floor or the dimly lit stair. At least 50,000/100,000/50,000 should be carried. These terms, which are also used below, have the following meanings: $50,000 limit for bodily injuries to any one person arising from a single accident; $100,000 limit for all persons receiving bodily injuries in a single accident; $50,000 limit for all property damage caused in a single accident. Similar insurance should be carried on all properties owned, in addition to the home, which is handled differently, as pointed out below.

Workmen's compensation. This need be carried only when the physician operates a structure or his employees handle certain types of tools, or under other circumstances required by state law. He should give his attorney the full facts and obtain a written opinion regarding the necessity or non-necessity of such insurance. In any event, an employer's liability policy or an endorsement to one of the other types of liability policies mentioned herein may be needed as protection against civil liability arising from other than under compensation statutes to employees. Such other policies frequently exclude injuries to employees, which must be covered by proper insurance.

Comprehensive personal liability. This covers legal liability arising from home accidents and from personal acts of oneself and members of one's family, such as slicing a golf ball and mistaking a farmer's cow for a deer. At least 50,000/100,000/50,000, as explained above, should be carried.

Automobile liability. The largest liability limits obtainable should be carried — at a very minimum, 100,000/250,000/50,000, and preferably even more than $50,000 for property damage (one could collide with a tank truck and burn up an entire suburb). Comprehensive, medical and emergency road service are comforting to have, but their absence would not cause bankruptcy in the event of loss. Similarly, a physician can afford to carry a $250 deductible or other low-cost collision coverage, instead of the more common and more expensive types. He can absorb the small property loss, if necessary, but he cannot act as banker against the heavy liability hazards.

Property-Insurance Coverages

I recommend particularly the following types of policies:

Personal property floater coverage. This is the first of the nonliability coverages to be discussed. This can well be carried with a nonconference company at a deviated rate on a three-year or five-year basis, preferably, again, with a $50 or $100 deductible provision. A conference company is one which adheres to a standard rate fixed by an actuarial bureau. A company not bound by such an arrangement is frequently called a "nonconference" company and often writes such insurance at a rate "deviated" from, or lower than, the standard rate — either by simply charging a smaller premium or by returning a dividend of 15 to 25 per cent of the premium at the end of the policy term. Of course, the stability of such a company should be established.

A floater policy protects against loss of personal property (other than office property, unless this is added by endorsement) by fire, theft, disappearance and other casualties at home or away from home. If office furniture and equipment are not added to this policy by endorsement simple fire and extended coverage insurance is generally adequate upon the office furnishings. I have never heard of the theft of an x-ray machine.

Fire and additional extended coverage. This should be carried on any real estate that the physician owns or in which he has any interest, generally again upon a three-year or five-year basis. Again, this can frequently be obtained at a deviated rate, as explained above. However, coinsurance, which may save premiums now but prove expensive in the event of loss, should be avoided. Coinsurance is insurance in which the company bears the entire risk up to the policy limit—*provided,* however, and this is important—that such insurance is in the full value, or proportion of value required, of the property insured. If such insurance is carried in the amount of only half the value, the company pays for only half the loss. In this day of rapidly mounting values and particularly when reconstruction costs greatly exceed cash market values, coinsurance can easily lead to argument on the occurrence of a loss.

Health and Accident Coverages

In life one has to take certain chances and to assume certain risks. A good place to do so is with this form of insurance to save the premiums that must otherwise be expended. As yet, disability insurance has not been designed for the needs of the professional man. So long as either an attorney or a physician can see people, or even converse with them, he is not totally and permanently disabled, even though he is confined to a wheel chair or to bed. He is far better off, as a rule, if he saves his premiums than if he buys coverages that do not fit his needs.[3,4]

The short-term loss the physician can absorb himself. The rare situation of an extended or even of true permanent disability he could not—but he must decide if the gamble is worth the premium. If he decides to insure, to hold down expense he should purchase nothing but lifetime protection against disability, defined in terms of his occupation, purchased upon a noncancellable basis from a company of good repute and accept a long waiting period—thirty, sixty or even ninety days—after the origin of the accident or disease. Some group plans offer reasonable protection in a seminoncancellable form, whereas other policies are subject to definite criticism. Since disability policies vary widely, even within a single company, each must be analyzed separately when presented. Normally, however, I prefer sound health and accident policies over disability riders added to life-insurance contracts, even though the latter may provide for lifetime reimbursement in the event of total permanent disability.

Life Insurance

Life insurance is in quite a different category from health and accident coverages. Such insurance should be the first major purchase by a physician. It is the only means by which he can buy a ready-made estate on the installment plan to protect his wife and children in the event of his premature death.[5] This is no time, in his early years, for frills—such as educational policies for the children, retirement-income insurance or high-cost contracts. He should buy, as quickly as possible, $100,000 of convertible term insurance with a sound major company with which he will be willing to carry his insurance program for the rest of his life—and let the dividends reduce the insurance cost. As soon as he can afford to do so, he should convert to ordinary life insurance and let the dividends, if his means are ample and the policy is of a participating type, accrue to pay up the insurance more quickly. He has thus given his family immediate protection; he has guarded against the risk of later uninsurability; and later, as means permitted, he has embarked upon a retirement program. As funds increase, the physician may also add additional contracts with still greater savings features. And, by all means, he should include a waiver of premium provisions in the event that disability should prevent the discharge of his premium obligations.

Chief terminology. The two major kinds of life insurance evolve from the nature of the company issuing the policy. The majority of life insurance is issued by mutual companies in contracts termed "participating policies," which simply means that a portion of the premium is returned annually in the form of dividends. Such dividends can be used to reduce the premium, to shorten the premium paying period or to add to the policy protection.

Representative policies. Policies issued by stock companies are "nonparticipating"—that is, they are figured on a net cost basis and return no dividends. The gross premiums quoted on such insurance are always lower, but the question of ultimate net cost

depends on the particular company and its experience over a period of years.

The premium that the insured pays is divided into two parts: net premium, which is, in turn, subdivided into current-year mortality element and current-year increase to policy reserve; and expense loading. It is obvious that the mortality element, or risk of death, increases each year. That is one reason why insurance costs less when taken at an earlier age. Not only is the mortality risk less but also the company has longer use of the money with which to secure earnings and thus to increase the policy reserve. These earnings from the reserve are carefully computed with the mortality element to establish a "level premium," which is not subject to increase as the insured grows older.

Obviously, then, since the cost of the mortality feature will be the same at the age of thirty-five whether the insured carries term insurance, ordinary life or some form of endowment insurance, it is apparent that the amount of money left from the premium payment to accumulate at interest depends on the size of the premium paid. If the mortality element at the age of thirty-five is $10 per $1000 and the expense loading is $2, and the insured pays only $12, there is nothing left to go into the reserve. If he pays $25, there would be $13 left; if he paid $50, there would be $38. In each case there would be the same amount of life-insurance protection *during the policy period;* the difference would be in the amount of savings.

The different types of contracts, their cost as between an excellent mutual and an excellent stock company at present rates, guaranteed cash values at the age of sixty-five and projected dividends are presented in Table 1. It will readily be seen that the higher premium contracts accumulate greater cash values but provide, proportionately, far less protection. At the age of forty $2500 a year in premium payments will buy more than $90,000 of ordinary life insurance, whereas it will buy only $65,000 of twenty-payment life insurance, which, however, at the end of twenty years, will have greater loan or cash surrender values. Therefore, the goal for the young man normally should be large protection and small savings features, and that for the older man thinking of retirement, larger savings features and less protection.

TABLE 1. *Various Life-Insurance Contracts (All Figures Based on Units of $1,000 of Life Insurance).*

	Age of Insured	Gross Premiums	Average Projected Dividend	Premium	W. P.*	W. P.*
		PARTICIPATING	1st to 20th yr.	NONPARTICIPATING	PARTICIPATING	NONPARTICIPATING
	yr.	$	$	$	$	$
10-yr. convertible term insurance†:	25	8.50	3.18– 4.26	6.59	0.32	0.42
	30	9.98	3.72– 5.08	7.01	0.43	0.52
	40	15.54	5.44– 6.44	10.60	0.94	1.00
	50	28.08	7.07– 9.20	20.63	2.40	2.83
Ordinary life insurance (payments as long as one lives):	25	20.60	3.60– 8.53	16.56	0.45	0.59
	30	23.73	4.24– 9.49	19.10	0.57	0.73
	40	32.55	6.15–12.10	26.67	0.99	1.27
	50	46.99	7.93–14.80	39.72	1.88	2.61
20-payment life insurance:	25	33.79	3.65–10.75	28.16	0.32	0.48
	30	36.95	4.11–11.50	30.78	0.41	0.52
	40	44.89	5.90–13.18	38.13	0.85	1.06
	50	56.69	7.96–14.62	49.57	1.94	2.70
Retirement income at age 65,‡ maturing as cash endowment:	25	34.43	3.67–11.09	30.79	0.64	0.79
	30	41.07	4.30–12.48	36.77	0.83	1.02
	40	62.54	6.44–17.28	57.60	1.51	1.98
	50	112.22	9.40–23.36	106.72	3.11	4.83

*W. P. = waiver of premium cost per $1000 of insurance.

†In some companies the insured must convert within the eighth year under a 10-year convertible term policy.

‡$2500 paid each year beginning at age 35, with one company, would give an insurance feature of $75,000 if the insured dies prematurely. At age 65 the total cash value, including dividends, would amount to $108,250 and provide a life income of $666.82 a month on a ten-year certain basis or $595.37 on an installment refund basis.

Life insurance has great values, which are too numerous to be considered at length. Its settlement options, for one thing, afford flexible mediums for providing fixed payments to one's widow or children without trustee's expenses. But life insurance also has its limitations. For a physician to embark on a top-heavy program, neglecting all other forms of retirement accumulation—unless he is otherwise incapable of wise saving—is also not to be commended. Nor, under today's rates, can annuities be recommended for purchase except in rare cases when their purchase may be advised by an estate analyst.

Wills and Trusts

The next major step to be considered in the field of estate planning is that of testamentary instruments—

or, in other words, the legal papers by which one provides for the care of his survivors. For the young physician, this means two wills—one for himself, and one for his wife, with testamentary trust provisions to guard against the death of both parents while one or more children are minors.

I become greatly irked when I hear of lawyers blithely addressing luncheon clubs about estate problems and exhorting the merits of a short, simple will. Such an instrument means simply that one has dumped his problems into the lap of the probate court and that the judge, a stranger, must guess what one's wishes would be, since one failed to be explicit.

When the physician is first entering practice, this instrument (except when parental care is necessary) should usually leave everything to the wife with only the qualifications that may be necessary for her protection. In the event of her death a trustee should be designated to handle the property for the children until they come of age.[6] Preferably, this should be a substantial banking institution in the state where the children will be living. A guardian should be selected to rear the children who may then be minors, if both parents are deceased. This should be, preferably, a relative whose age and tastes are similar to those of the parents. Arrangements should be made for the trustee to pay sufficient funds to the guardian for the maintenance and education of the children. Life-insurance proceeds remaining after the widow's death should normally be added to the trust corpus for greater flexibility in total administration.

Such a will must provide for equalizing the shares of children fairly, since they will usually be of different ages when their parents die and will have received varying years of parental support. One must analyze the possible careers they may follow and, if a male child elects a long period of college training, the testator should make fair provision for a female child who may marry at the age of eighteen years. The parent must also distinguish between desirable security and destruction of incentive; between alleviation of hardship and creating an Old Man of the Sea that may destroy a daughter's marriage, when her husband believes that his family leadership has been undermined by her financial independence or when she becomes more eager to walk out after a quarrel than to kiss and make up.

TABLE 1 *(Concluded).*

GUARANTEED CASH VALUE AT AGE 65 PARTICIPATING $	PROJECTED DIVIDEND ADDITIONS AT AGE 65 $	GUARANTEED CASH VALUE AT AGE 65 NONPARTICIPATING $	PAID-UP INSURANCE AT AGE 65 PARTICIPATING $	PAID-UP INSURANCE PURCHASED BY DIVIDEND ADDITIONS $	PAID-UP INSURANCE AT AGE 65 NONPARTICIPATING $
628.11	542	597	790	682	793
600.35	469	569	755	590	755
522.10	323	492	656	407	653
393.94	190	365	495	239	484
795.30	544	754	1000	684	1000
795.30	467	754	1000	587	1000
795.30	327	754	1000	411	1000
586.81	194	550	1000	244	1000
1623.00	746	1664	1623	746	1664
1623.00	640	1664	1623	640	1664
1623.00	448	1664	1623	448	1664
1623.00	274	1664	1623	274	1664

TAX-SAVINGS FACTORS

When one has begun to accumulate a substantial estate the emphasis may then—but not until then—shift toward tax savings. The principles of tax savings are basically simple, although the proper carrying out of such principles is enmeshed with difficulties. To save income taxes one must split income between more low-base taxpayers. Since individually earned income cannot be so apportioned out or split, except from the split-income provisions of the income-tax law, gift or sale devices may be used to shift investment income to other members of a family, one or more corporations, or to one or more trustees.[6] Thus, if a father is in a 60 per cent income-tax bracket, any rental income from investment property leaves him only 40 per cent. By conveying such property to his

two sons, or to a trustee, with a presently low or nonexistent tax rate he may cut the tax consequences by half or more, leaving larger net sums for family use. What may be entirely appropriate in one case may be completely inappropriate in another. The devices used must be carefully selected with expert help and skillfully drafted.

In addition to income-tax savings sound planning requires consideration of federal estate taxes, state inheritance taxes, administration expenses and shrinkage that might result from forced liquidation of estate assets at figures below their values to pay claims and other charges. For estate-tax purposes all property in which the decedent had an interest at the time of his death is included—even joint-tenancy property and life insurance that he has made expressly payable to his wife or children. The first $60,000 of such an estate is exempt from federal taxes, the rate thereafter beginning at 3 per cent and rising to a maximum of 77 per cent. State inheritance taxes usually increase in proportion to the size of the bequest and the remoteness of kinship of the legatee. All such items may substantially reduce a poorly planned estate.

One method of accomplishing savings in estate taxes is the use of the marital deduction, or split-estate method, in the physician's will. He may leave up to half his estate outright to his widow free of estate tax, those assets then being subject to tax in her estate if they remain at that time. The other half he may leave to a trustee in such a way that his widow may receive the income of it, if that is what he wants to accomplish. That half only will be taxed in the physician's estate, but it will escape taxation in his widow's estate. Various methods of using all or portions of the marital deduction will suggest themselves, depending on the situation.

Another method of reducing potential estate taxes is by giving away portions of the estate while one is living. By proper planning, one can give large portions to his children during his lifetime with no tax consequences—and, in any event, a gift tax will usually be far less than the comparable estate tax on the same property or money. There are several reasons for this: each spouse has a $3000 annual exemption for each donee; each spouse, in addition to these annual exemptions, has a $30,000 gross exemption, which may be consumed before any gifts are subject to gift tax; since both estate taxes and gift taxes are progressive, the making of a gift normally takes such property from the top of the applicable estate-tax brackets and moves it down to the lowest gift-tax brackets; and the gift-tax rate is only three fourths of the estate-tax rate on property in the same tax bracket. The warning must be advanced, however, to make these gifts only with the most careful of expert guidance.

Nature and Method of Practice

The physician must also consider the method in which he is going to conduct his professional practice: as an employee of a corporation, a clinic or a partnership; as a sole practitioner; or as a partner in a clinic or other entity. Such a decision depends largely on the physician himself—his type of practice, his personality, his energy, his sociability and similar factors. No estate analyst is going to tell him to throw up his job and seek another. Estate planning is undertaken by lawyers specializing in specific phases of the law—not by psychoanalysts or employment counselors. It would be presumptuous to attempt to advise the very person who knows more about himself and his adaptability to these factors than any third person.

However, a few recommendations must be made. The first is that any lasting relation must be built on solid rock. It must be established between persons who both respect and like each other thoroughly, who are equally energetic and willing to assume responsibility and whose integrity is above reproach. It would be better if they then lived in different parts of the town and did not visit back and forth socially. Even in large clinics, intraclinic social affairs seldom work out happily.

A clinic must have a sound program for pensions and advancement if it expects to retain qualified personnel on a nonpartner basis. In this regard, I strongly counsel against the use of an "association" or the like at the present time. The experiments in this direction are still fraught with danger, of an explosive quality—such as taxation of all funds used for distribution, other than as salary payments, to the members on a regular corporation-tax rate plus possible 75 per cent or 85 per cent surtax penalties as a personal holding company. There are enough safe and orthodox technics so that dangerous experimentation can profitably be left to the more venturesome person, who is willing to pay heavy penalties if he guesses wrong.

A partnership should be spelled out in writing with sufficient detail to clarify any reasonably probable contingencies. A sound buy-and-sell agreement,[7] particularly if funded by life insurance, has its place in such a procedure. These matters can be worked out by an expert when the details and problems are known.

Necessity of Regular Audits

There is a final suggestion that may be helpful to physicians. It is suggested that each practitioner or partnership engage a certified public accountant on an annual basis to make a monthly audit and an annual report, as well as to prepare the tax returns. He not only will detect, as a rule, employee pilfering or waste in early stages, but also will correct habits of permitting large receivables to accumulate and keep the physician out of difficulty with the Government. But the physician must remember that the accountant is not an estate analyst and is no more qualified than a life-insurance underwriter on matters of estate planning. Each man has a value within his field, but not beyond it.

SUMMARY AND CONCLUSIONS

Estate planning, and planning for economic security are therefore lifetime projects—not one-shot affairs. The expert can start the physician on a proper path, or redirect his steps if they have strayed. From time to time, he can help the physician to check his bearings. But it is for the physician, himself, to set his goal and to strive for its fulfillment. In this, however, he must be certain that he does not substitute false idols for those worthy of him. The companionship of one's wife, the laughter of one's children, are of far greater value than mere monetary accomplishments. The respect of one's colleagues and of the community are precious things. Happiness cannot be bought with money alone, but only with an appreciation of life and the living of a philosophy that is true to one's own character. Those objectives should be reanalyzed as frequently as plans for financial success and economic security.

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MEDICAL PROGRESS

Current Concepts in Digitalis Therapy (Continued)*

BERNARD LOWN, M.D.,† AND SAMUEL A. LEVINE, M.D.‡

BOSTON

Rising Incidence of Digitalis Intoxication

With the introduction of the purified glycosides it was expected that the incidence of intoxication would diminish. The patient on such maintenance therapy is assured a constant dosage because the uncontrollable variation in the potency of digitalis-leaf preparations is removed. The converse, however, has been true. Many recent reports indicate a mounting frequency of digitalis poisoning.[46,69-74] Digitalis is becoming a significant factor in cardiac death. The explanations given are that the glycosides are more toxic than leaf and that the premonitory symptoms are infrequent or absent. Both these contentions are without clinical substance. The pattern of toxicity is the same irrespective of the drug employed. The therapeutic-toxic ratio, the only valid way of comparing digitalis compounds, is approximately the same for nearly all these drugs.

The increasing frequency of intoxication, we believe, is related to the current manner of digitalis usage and the changing methods in the management of patients with congestive heart failure.

With the purified glycosides rapid intravenous digitalization has become a common practice. As a rule this route is not justified. Digitalis intoxication more often follows intravenous medication; furthermore, the oral route permits prompt and effective achievement of the same result. A more serious problem derives from dogmatic oversimplification in dosage prescription. A single-dose method for digitalizing with digitoxin has been promulgated. Patients are given 1.2 mg. of digitoxin at once and are maintained on 0.2 mg. daily. The administration of equivalent amounts of digitalis leaf or tincture is not possible because of the high incidence of prompt gastrointestinal upset from direct local irritant action.[75] This method has gained vogue because of its simplicity. The practice is of little hazard to the ambulatory cardiac patient with early failure, especially since 1.2 mg. of digitoxin, as shown by DeGraff and his associates,[58] is a subdigitalizing dose in most cases. Intoxication, however, has been repeatedly observed even with this dose.[27] For the patient with serious cardiac disability the dangers multiply. Much of the toxicity reported since the introduction of the glycosides has been due to digitoxin. The validity of the single-dose method holds for the "average" cardiac patient. Clinically, such patients are seldom encountered. This approach creates pharmacologic rigidity for the patient with congestive heart failure. Until a simple procedure has been devised for predicting digitalis requirements responsible practice demands empiric individualization in dosage schedule for each patient.

Another factor responsible for the increase in toxicity is the expanding life span of patients with heart

*From the Medical Clinic, Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School.
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†Formerly, assistant in medicine, Peter Bent Brigham Hospital.

‡Clinical professor of medicine, Harvard Medical School; physician, Peter Bent Brigham Hospital.

disease. Antibiotics, salt restriction, surgery and application of newer physiologic principles to therapy have contributed to the lengthening of life. The patients who are salvaged by these means have prolonged life expectancies with greater opportunity for even severer heart failure to develop. It has already been emphasized that these sicker patients are more prone to toxicity.

Perhaps the most important reason for the rise in the incidence of digitalis intoxication is the increasing dependence of treatment on electrolyte manipulation. Restriction of salt ingestion and administration of mercurial diuretics, ammonium chloride, cation-exchange resins, carbonic anhydrase inhibitors and cortisone are becoming part of the therapy for failure. All these measures induce changes in electrolyte metabolism and may alter the threshold of the myocardium to digitalis intoxication. Such electrolyte shifts will increasingly complicate digitalis treatment of congestive heart failure. This problem is dealt with in the next section.

Body Potassium and Digitalis Intoxication

General Considerations

The importance of potassium ions for heart function was pointed out by physiologists near the turn of the century.[76-78] These observations were overlooked or neglected until clinical associations called attention to them. Of all the ionic alterations encountered in man, those due to potassium have the most pronounced effects on the heart. One of the properties that differentiate potassium from other cations is its high rate of mobility across cell membranes.[79] This may be the basis for the critical role of potassium in muscular excitability and conductivity. It appears that the migration of potassium ions links the electric phenomenon of excitation with the biochemical process of energy release essential for the mechanical event of contraction.

Changes in body potassium content when accompanied by alterations in extracellular concentration are reflected in the electrocardiogram. The effects of both hyperkalemia and hypokalemia on the heart have been adequately reported.

A profound relation exists between digitalis and potassium. Digitalis affects the potassium concentration of the myocardial cell. There is general agreement that toxic doses of digitalis liberate potassium from heart muscle.[80,81] No agreement exists on the effects of therapeutic doses of digitalis on cellular potassium concentration. The whole range of possibilities from no change in potassium[80,81] to cellular loss[36] and gain[34,35] has been reported. Boyer and Poindexter[35] attribute the therapeutic action of digitalis to restoration of cellular potassium and improved cellular hydration. The resemblance between digitalis and adrenal steroids in chemical structure has prompted the suggestion that there may also be a similarity in function in that digitalis acts to maintain potassium within the cell.

A converse relation also exists: changes in potassium concentration influence the action of digitalis. At present, data are available primarily on the toxic effect. When the isolated striated muscle of a frog is treated with ouabain there is an initial rise in tension and heat production, followed in time by loss of excitability. Immersing the muscle in Ringer's solution, which contains potassium, causes a reversal of toxicity.[82] When rabbits are given potassium salts the lethal dose of ouabain is increased. Similarly, when the isolated duck heart is perfused with fluid of high potassium concentration the toxic action of digitalis is inhibited.[83] This inhibition may be due either to depression of myocardial irritability by potassium or to the interference with the escape of cellular potassium when the heart is exposed to large amounts of digitalis.

In man potassium salts reduce or abolish ventricular extrasystoles and at times reverse paroxysms of ventricular tachycardia.[84-86] The effectiveness of potassium does not continue on the precipitating factors of the arrhythmia. Sampson et al.,[87] who first introduced potassium in the treatment of clinical arrhythmia, noted that its action is more effective when the disturbance of rhythm is caused by digitalis. Other investigators have confirmed that potassium is promptly effective against many of the arrhythmias produced by digitalis.[44,88,89] It has been reported that potassium salts also eliminate the symptoms of overdosage and rapidly promote a sense of well-being in patients with digitalis poisoning.[88]

Potassium Metabolism in Congestive Heart Failure

Electrolyte and water abnormalities in congestive heart failure are due both to derangements in heart function and to the therapeutic procedures in current use.

In heart failure the excretion of sodium is impaired. In the usual case of failure, although total body sodium is significantly increased, the serum concentration is moderately lowered.[90,91] The hyponatremia not only is the result of dilution but probably also involves intracellular shifts of sodium. The serum potassium level remains normal, and the chloride concentration is slightly increased, with a tendency to acidosis.

There is evidence that during the development of failure potassium is lost from the body. Administration of large quantities of sodium and potassium salts to patients with heart failure results in potassium retention without weight gain.[90] A positive potassium balance has been observed in patients recovering from failure.[92,93] This positive balance may reflect the replacement of cellular potassium deficits sustained during the development of failure. Measurements of exchangeable potassium carried out with the radio-

active isotope dilution technic have disclosed a reduction in total body potassium in heart failure.[94] This occurred even though extracellular fluid was absolutely increased and the serum potassium level remained normal. These facts imply internal body electrolyte shifts involving both the extracellular and intracellular compartments. Disturbances in concentration and distribution of the major cellular cation, potassium, are therefore associated with the evolution of congestive heart failure.

The loss of body potassium during failure affects also the chemical topography of heart muscle. As the heart increases in weight there is a reduction in the cellular concentrations of potassium, phosphorus and creatine.[95-97] The decrease in potassium is most marked in the chambers of the heart that are failing.

Many factors contribute to the liberation of heart-muscle potassium in failure. Anoxia, acidosis, edema and prolonged exercise are known to induce potassium loss.[70,98-100] Overwork has been held responsible for the release of cellular potassium, and this in turn is believed to predispose to muscular fatigue and failure.[98,100]

The patient with failure is additionally the subject of nutritional problems. Loss of appetite, anorexogenic drugs, unpalatable diets, impaired gastrointestinal absorption and deranged liver function are some of the factors that favor a negative nitrogen balance. During fasting both nitrogen and potassium are lost from the body in a ratio reflecting their respective concentrations in the muscle. To restore muscle protoplasm potassium is essential. In rats potassium deprivation induces myocardial lesions and causes death from congestive heart failure.[101]

Present-day therapy also contributes to the deranged electrolyte picture. It has been stated that electrolyte abnormalities in the serum are absent in the untreated patient.[102,103] Low-salt diets and diuretics are the chief agencies that disturb normal electrolyte equilibrium. The injection of mercurial diuretics promotes the excretion of a bicarbonate-free chloride-rich urine. After administration of mercurial diuretics the urinary chloride and potassium concentrations are significantly higher and the sodium lower than their respective values in the serum. With extensive diuretic therapy hypochloremic hypokalemic alkalosis may result.[27,104] The composition of the diuretic urine and the lack of change in serum sodium and potassium levels indicate that potassium leaves while sodium enters the cellular compartment. The edematous patient who has been on rigid salt restriction for a long time is more likely to respond to mercurial agents with increased potassium diuresis.[105] The patient with advanced failure is therefore more likely to experience serious losses of potassium.

The protracted administration of ammonium chloride by itself may result in potassium depletion. Usually, ammonium chloride is employed to synergize the action of mercurial diuretics. The excretion of potassium is increased by such pretreatment. Potassium concentration in the diuretic urine is raised by about 15 milliequiv. per liter when ammonium chloride is given to enhance the action of mercurial diuretics.[105] Recently introduced methods for removing sodium from the body, such as the cation-exchange resins and Diamox, also have pronounced effects on the potassium balance.

In patients with heart failure the underlying pathologic process and the therapeutic regimens for its management constitute the two general categories of factors that deplete both cellular and myocardial potassium. It is unknown to what extent potassium depletion contributes to the biochemical lesion and aggravates the clinical state of congestive failure. It has been demonstrated, however, that the loss of potassium significantly affects the body's threshold to the toxic action of digitalis and may be an important cause for the rising incidence of digitalis toxicity.

Postmercurial Redigitalization

Evidence that potassium loss from the body may precipitate digitalis intoxication was first gained in a study of the postmercurial redigitalization phenomenon. From twenty-four to forty-eight hours after diuresis a digitalized patient may experience nausea, vomiting, giddiness, headache and considerable weakness. Electrocardiograms may demonstrate any of the changes that occur with an overdose of digitalis. Schnitker and Levine[106] attribute these manifestations to the mobilization of digitalis-laden edema fluid by the diuretic agent. They assume that as much as 0.1 gm. of digitalis leaf may be present in a liter of edema. This is now the prevailing view explaining the onset of symptoms and signs of digitalis overdosage after diuresis.

There are serious objections to the digitalis mobilization theory. If the phenomenon were due to the fact that more digitalis reached the heart from fluid depots, its occurrence should relate to the magnitude of the diuresis. This is not so. The onset seems to be related to the administration of ammonium chloride and to the degree and duration of salt restriction. Furthermore, giving large additional doses of digitalis to patients consistently experiencing postmercurial redigitalization frequently does not precipitate toxicity. Symptoms and signs are readily preventable if potassium is given in conjunction with the mercury injection. It seems probable, therefore, that excretion of body potassium rather than mobilization of edema-laden digitalis is the responsible factor.

This hypothesis was tested clinically. Nondigitalized patients were given acetyl strophanthidin, an ultrarapid-acting, digitalis-like preparation that is eliminated in two or three hours, both before and after a mercurial-induced diuresis. A decrease in threshold to the toxic effects of digitalis was noted only when the diuresis was accompanied by significant potassium

excretion. The following cases illustrate this experience.*

H.D., a 69-year-old diabetic man, had coronary-artery and hypertensive cardiovascular disease, with atrial fibrillation and right-sided and left-sided failure. On 2 occasions the intravenous injection of 1.2 mg. of acetyl strophanthidin gave identical responses (Fig. 3*A*). Maximum

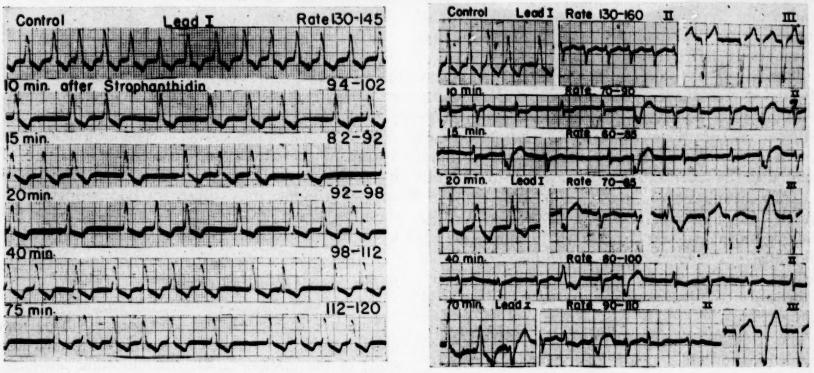

FIGURE 3. *Electrocardiograms in H. D.*

The effects of 1.2 mg. of acetyl strophanthidin given intravenously are shown in A. *Maximum slowing occurred at fifteen minutes, with restoration of control rate at ninety minutes. There was no evidence of digitalis intoxication.* B *shows the effects of 1.2 mg. of acetyl strophanthidin twenty-four hours after a diuresis with potassium loss. Multifocal ventricular premature beats appeared in five minutes. Toxicity was evident for about ninety minutes.*

ventricular slowing occurred within 15 minutes. The effect waned within 1 hour, and control rates were restored after 90 minutes. There was no subjective evidence of digitalis overdosage. The 3d digitalization was carried out some days later. It followed a diuresis produced by 2 cc. of mercaptomerin, which had been supplemented by ammonium chloride. This time the response to 1.2 mg. of acetyl strophanthidin was qualitatively different (Fig. 3*B*). Within 5 minutes of the injection multifocal ventricular premature beats appeared, with runs of bigeminy and trigeminy. One hour after the strophanthidin the patient experienced nausea and vomiting. Toxicity persisted for about 90 minutes, whereas the therapeutic slowing continued for

*These cases, which were studied at the Montefiore Hospital and are reported in full elsewhere,[107] are included with the kind permission of Dr. Louis Leiter.

4 hours. Study of the potassium balance revealed a loss of 83 milliequiv. after the ammonium chloride and mercaptomerin, without any significant changes in the serum potassium concentration.

A.R., a 20-year-old woman with mitral stenosis, had normal sinus rhythm and right-sided and left-sided failure. On 2 occasions, 1 month apart, she was digitalized with small fractional doses of ouabain to end points of mild toxicity. Each digitalization followed a mercurial-induced diuresis that resulted in excretion of significant quantities of potassium (Table 1). The atrial mechanisms at the time of the 2 tests were different, and yet the requirements of ouabain were nearly the same (Fig. 4*A*). With 0.6 mg. and 0.7 mg. of ouabain nausea, vomiting, changing atrial pacemakers and rare ventricular premature beats developed. The arrhythmias persisted for several hours.

When ouabain was given in an identical manner but after a positive potassium balance, achieved by the ingestion of 7.5 mg. of potassium chloride daily for 10 days, the dose for toxicity was nearly doubled. Ventricular extrasystoles were not observed (Fig. 4*B*). This occurred despite a 20 per cent reduction in weight. After 1.2 mg. of the drug the patient exhibited the same toxic end point as previously,

TABLE 1. *Successive Digitalization with Fractional Doses of Ouabain to the Earliest Electrocardiographic Evidence of Intoxication.**

DATE	DRUG	POTASSIUM BALANCE	POTASSIUM SERUM	BODY WEIGHT	AMOUNT OF OUABAIN FOR TOXICITY	DURATION OF TOXICITY
		milliequiv.	*milliequiv./liter*	*kg.*	*mg.*	*hr.*
May 3	Mercaptomerin (2 cc.)	−100	5.1	44	0.7	4
June 3	Mercaptomerin (2 cc.)	− 70	3.6	39	0.6	3
June 13	Potassium chloride (7.5 gm. per day for 10 days)	+210	5.2	35	1.2	1

*On May 3 and June 3 ouabain administered 24 hr. after the production of negative potassium balance by means of mercurial-induced diuresis. Serum potassium values on morning of digitalizations not altered by previous mercury diuresis. On June 13 ouabain again given, this time after ten days of potassium supplementation and positive balance (see also Figures 4*A* and *B*). *Note increased tolerance to ouabain afforded by administration of potassium.*

and with a total dose of 1.3 mg. she experienced nausea and vomiting. This time toxicity lasted for only 1 hour.

Two patients in similar studies who did not sustain losses of potassium after diuresis showed no changes in threshold to the action of acetyl strophanthidin.[107]

The postmercurial redigitalization phenomenon may be defined as a state of increased myocardial sensitivity to the toxic properties of digitalis resulting from a negative potassium balance precipitated by diuretic therapy. In its presence digitalis should be discontinued and potassium administered by mouth until the evidence of overdosage disappears. Serious disturbances of rhythm and even death will be prevented if diuretics are withheld when the patient gives any evidence of digitalis intoxication.

Potassium Losses Induced by Means Other than Mercurial Diuretics

Losses of potassium, irrespective of cause, potentiate the toxic action of digitalis. Both desoxycorticosterone acetate and cortisone may produce negative potassium balance and alter the threshold of the heart to digitalis.[44,107] We have observed a case in which postmercurial redigitalization developed only after cortisone had been started. Symptoms and signs were controlled by oral potassium supplementation. Marked disturbances of rhythm may result from small doses of digitalis when patients have sustained chronic potassium depletion through either the renal or the gastrointestinal route. In these patients, when the serum potassium level is depressed, even small amounts of digitalis can prove fatal.

Generally, there is no reliable correlation between serum potassium concentration and digitalis requirement. The increased sensitivity that at times follows diuresis is not reflected by the serum level. The serum

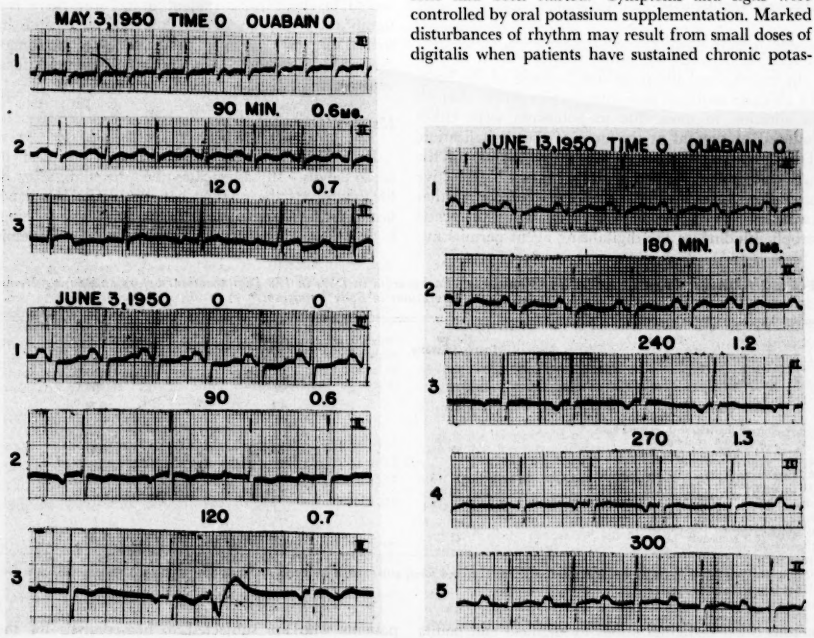

FIGURE 4. *Electrocardiograms in A.R.*

A and B represent two different occasions when ouabain was given intravenously. In each a prior mercurial injection had been followed by substantial diuresis and potassium excretion (Table 1). 1 is the control tracing. 2 and 3 were obtained thirty minutes after 0.6 and 0.7 mg. of ouabain. Nausea and vomiting followed both digitalizations. After 7.5 gm. of potassium chloride daily for ten days ouabain was again administered with the same dosage schedule as previously. Toxic changes did not occur until thirty minutes after a total dose of 1.2 mg. (3). Nausea and vomiting followed 1.3 mg. (4). The changing pacemaker disappeared within thirty minutes (5), and the first-degree block was absent after another thirty minutes. (Note the protective action of potassium.)

potassium value is usually normal in the presence of digitalis intoxication. When the manifestations of overdosage are reversed with potassium there is no significant or sustained rise of the serum potassium concentration. A relation, however, exists between body potassium balance and the heart's sensitivity to digitalis. This sensitivity increases with a negative balance and decreases with a positive one.

Animal Hemodialysis

The studies cited above do not establish with finality a relation between the myocardial threshold to digitalis toxicity and the potassium balance of the body. In all cases multiple and complex electrolyte changes in addition to those due to potassium were either induced or present at the time of the digitalization. This limitation can be overcome by the use of the artificial kidney. Hemodialysis makes possible selective alterations of individual ions while controlling other variables. Furthermore, the availability of acetyl strophanthidin* as the digitalizing agent permits numerous discrete digitalizations to identical end points in the course of a single day. The combination of these methods enables one to effect biologic titration of digitalis requirement while body potassium is being increased or decreased.[63,108]

The relation of digitalis to potassium was investigated in 11 dogs by means of the artificial kidney and acetyl strophanthidin. During this study 178 discrete digitalizations were carried out to identical end points of ventricular tachycardia. When the serum potassium was kept normal, the dose of acetyl strophanthidin for the production of toxicity with consecutive digitalizations at two-hour intervals remained constant. When the serum potassium was raised there was a striking increase in drug requirement, toxicity was of brief duration, and atria rather than ventricles appeared to be most affected. When potassium was removed from the body the dose of acetyl strophanthidin was materially reduced, and the duration of toxicity was significantly prolonged (Table 2). A further difference was the emergence of multifocal premature beats, bigeminy and bidirectional ventricular tachycardia (Fig. 5). Hitherto, such rhythms have not been induced with digitalis in the intact mammalian heart in situ.[47]

It can be concluded that dogs depleted of potassium respond to digitalis in a manner similar to that observed in the cardiac patient in failure: there is a significant reduction in the dose that will cause intoxication; toxicity once produced is of prolonged duration; and there is an appearance of multifocal ventricular rhythms.

Human Hemodialysis

Patients with renal shutdown are improved by hemodialysis. In some cases the procedure may be life saving. If the relation between digitalis and potassium described in dogs holds for human beings it should be demonstrable in the digitalized uremic patients who are subjected to hemodialysis for the correction of azotemia and hyperkalemia. The procedure should induce arrhythmias and atrioventricular-conduction derangements only in the group receiving digitalis. This, indeed, has been our experience.[109]

In 33 hemodialyses in 25 patients the bath potassium concentration was maintained for two hours of the six-hour procedure at 2 milliequiv. per liter. During this phase of potassium removal, serial electrocardiograms were taken. At the time of dialysis 16 patients were on maintenance digitalis, and 17 patients, constituting the control population, had not received any digitalis. The average reduction in the serum potassium level of 2 milliequiv. per liter was identical in the two groups. The populations were also comparable in age, sex and the etiologic background of the renal disease.

Over-all results are presented in Table 3. Of the 16 digitalized patients, 7 manifested intoxication. The

TABLE 2. *Dosages Required to Produce Ventricular Tachycardia in Dogs in 178 Digitalizations before and during Hemodialysis, with Alterations in Body Potassium.**

PERIOD	NO. OF DIGITALIZATIONS	AVERAGE SERUM POTASSIUM	DOSE OF ACETYL STROPHANTHIDIN REQUIRED FOR TOXICITY
		milliequiv./liter	*mg.*
Before dialysis	82	4.1	0.74
During dialysis, with normal bath potassium concentration (4.0 milliequiv. per liter)	55	4.3	0.47
During dialysis, with low bath potassium concentration (0.1 milliequiv. per liter)	19	2.1†	0.19
During dialysis, with high bath potassium concentration (8.0 milliequiv. per liter)	22	7.0	1.15

*Note the large dose of acetyl strophanthidin (1.15 mg.) needed when potassium is high and the small dose (0.19 mg.) when potassium is low.
†Extraction, 25 milliequiv.

*Kindly supplied by Eli Lilly and Company, Indianapolis, Indiana.

toxic rhythms were serious in 4 and minor in 3. The changes consisted of first-degree and second-degree

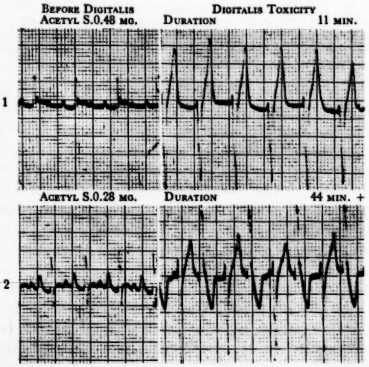

FIGURE 5. *Three Differences between Digitalizations during Hemodialysis When Potassium Is Kept Normal (Serum Level of 3.7 Milliequiv. per Liter as in 1) and When It Is Removed from the Body (Serum Level of 1.75 Milliequiv. per Liter and Extraction of 25 Milliequiv. per Liter, as in 2). There is a reduction in dosage, a prolongation of the duration of toxicity (in this experiment stopped by potassium administration after forty-four minutes) and production of multifocal rhythms (in this instance bidirectional ventricular tachycardia).*

heart block, atrial tachycardia with block, multifocal ventricular premature beats and unidirectional and multidirectional ventricular tachycardias. Six other patients who had not shown digitalis effect before dialysis demonstrated typical ST-segment scooping, T-wave inversion and QT-interval shortening after the removal of potassium. In the remaining 3 no changes occurred. Two of these were young people without antecedent heart disease who had congestive symptoms because of excessive fluid administration in the presence of complete renal shutdown.

TABLE 3. *Effect of Potassium Extraction on the Sensitivity of the Heart to the Toxic Action of Digitalis during 33 Hemodialyses in 25 Uremic Patients.**

Effect	No. of Cases
Digitalized patients:	
Toxicity	7
Digitalis effect	6
No change	3
Total	16
Nondigitalized patients:	
Arrhythmia†	1
No change	16
Total	17

*Note the great frequency of toxicity and digitalis effect in the digitalized patients.

†Atrial fibrillation.

In the 17 nondigitalized patients, potassium extraction resulted in no ventricular arrhythmias or atrioventricular-conduction disturbances. In 1 patient, who had experienced numerous sporadic episodes of atrial fibrillation, such a bout developed during dialysis. Potassium was not being removed when the atrial fibrillation started. Three of the 17 patients were also dialyzed at another time when they were not on maintenance digitalis. On this occasion all gave evidence of digitalis toxicity after the removal of potassium.

In 12 of the 13 patients with either digitalis effect or intoxication the serum potassium values were in the normal range. In 2 restoration of initial serum potassium level did not promptly abolish the evidence of digitalis intoxication.[109]

In this group of uremic patients, extraction of body potassium in the presence of maintenance or submaintenance of digitalis was sufficient to affect the reactivity of the heart and to evoke toxic manifestation.

Some Clinical Problems

Digitalis intoxication may simulate conditions that require digitalis for control, and, conversely, arrhythmias caused by various agencies besides digitalis may resemble digitalis intoxication. At times, prompt recognition of the underlying nature of the cardiac disturbance may be life saving. The following cases illustrate these points.

A.N., a 47-year-old man with mitral stenosis and regurgitation, for 8 years had had right-sided and left-sided failure with atrial fibrillation. During the year before admission he began to experience angina-like chest pain and became completely incapacitated. At the time of entry to the Peter Bent Brigham Hospital he was in severe failure, with marked orthopnea, chronic pulmonary congestion, ascites and ++++ peripheral edema. Shortly after admission digitalis was stopped because of the development of a nodal tachycardia. His condition, however, deteriorated rapidly. To assess the degree of digitalization, a digitalis tolerance test (described below) was carried out, indicating that he would benefit from full digitalization. This was accomplished within 24 hours. Thereafter, improvement was progressive. Within a 2-week period he lost 14 kg. of edema.

His improved status permitted the performance of valvuloplasty. Two days after the operation, notwithstanding increasing doses of digitalis, his heart rate accelerated and became regular. At this time he was cyanotic, moist rales were present at the lung bases, the systolic blood pressure was less than 90, and he appeared in peripheral vascular collapse. The idea of giving more digitalis was entertained. Since nodal tachycardias may be caused by digitalis overdosage, the decision was made to administer potassium instead. After 30 milliequivalents of potassium chloride had been given by vein the rhythm reverted to atrial fibrillation (Fig. 6). The patient's immediate status improved. The next day, without receiving any digitalis, he was nauseated and vomited, and the electrocardiogram exhibited a trigeminal rhythm.

The regularization of the ventricular response in digitalized patients with atrial fibrillation suggests overdosage. Toxicity should be suspected even when the ventricular rate has become significantly accelerated. When the heart rate increases the tendency is to give more digitalis. Whereas the majority benefit

from the additional dosage serious toxicity may follow in patients in whom the rapid heart rate is associated with regularization of the ventricles.

E.H.,* a 54-year-old man with calcific aortic stenosis, had been incapacitated by ever more frequent episodes of syncope and angina pectoris. He was admitted to the Peter Bent Brigham Hospital for an aortic valvulotomy. During the operation his blood pressure dropped for a brief period to shock levels, being restored by an intra-arterial transfusion of 1000 cc. of bank blood. During the day after operation there was another abrupt fall in pressure. Although he had

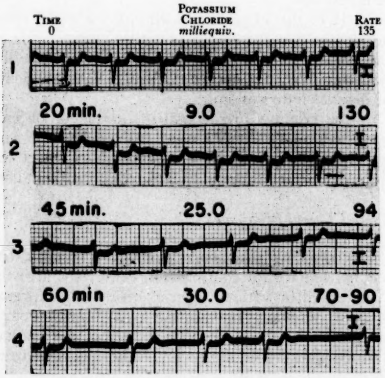

FIGURE 6. *Electrocardiograms in A. N.*

Nodal tachycardia developed forty-eight hours after operation while digitalis was being increased to control rapid atrial fibrillation.

Ventricular rate slowed during intravenous potassium administration (1). *Irregularization of rhythm (atrial fibrillation?) resulted after injection of 30 milliequiv. of potassium chloride* (2 *and* 3). *Serum potassium during this interval rose from 5.6 to 6.4 milliequiv. per liter. Sodium was unaltered at 126 milliequiv. per liter.*

a normal sinus rhythm before this second episode an electrocardiogram revealed the absence of P waves, irregular ventricular rhythm, intraventricular block and slight peaking of the T waves (Fig. 7). He had been digitalized be-

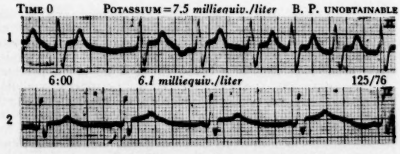

FIGURE 7. *Electrocardiograms in E. M.*

Shock developed twenty-four hours after aortic valvulotomy. Irregular rhythm, with slight peaking of the T wave, was due to hyperkalemia (1). *Normal sinus rhythm was restored, and the shock reversed by injection of hypertonic saline solution, glucose and insulin* (2).

fore surgery. During and after the operation he received both Pronestyl and quinidine. Intoxication with any one or more of these agents appeared possible. From the electrocardiographic standpoint the disorder suggested potassium poisoning. Notwithstanding his precarious cardiac status, he was given 300 cc. of 3 per cent saline solution in the course of 1 hour, followed by 700 cc. of 10 per cent glucose and 35 units of insulin. Improvement was remarkably rapid (Fig. 7). At the end of 1 hour his blood pressure rose to 124/78, and he began to have a copious diuresis. Thereafter, recovery was continuous and uneventful. A blood sample drawn before therapy revealed a potassium concentration of 7.5 milliequiv. per liter, corroborating the impression of hyperkalemia.

*This case is reported through the courtesy of Dr. Dwight E. Harken.

These patients illustrate two contrasting situations. Superficial examination of A.N. would have led one to give more digitalis. The patient, indeed, was showing an increasing heart rate, and the general circulatory state was deteriorating. Further digitalis might very well have proved lethal. The regularity of the rapid ventricular response in a previously fibrillating patient was the special feature that suggested overdigitalization. For that reason potassium was given and was effective.

In E.H. the lack of P waves again led the attending staff to the diagnosis of nodal rhythm caused by an overdose of digitalis. The administration of potassium was considered. However, the possibility of digitalis intoxication was dismissed for two reasons: in human beings digitalis intoxication does not cause intraventricular-conduction impairment; and when complete atrioventricular dissociation or nodal rhythm results from an overdose of digitalis, the ventricular response is usually regular. When it is irregular, interference from sporadic conduction of the atrial impulse is evident.

A slow irregular ventricular rhythm with intraventricular block and atrial paralysis strongly suggests potassium poisoning. This is to be considered even in the absence of the characteristic changes in the T contour. Advanced hyperkalemia may be present without peaked T waves.[110] In E.H. the rapid infusion of bank blood under pressure may have produced hemolysis and thus provided an exogenous source of potassium. The control of the hyperkalemic effects on the heart by the combination of hypertonic sodium solution, glucose and insulin permitted the kidneys to excrete the excess potassium without further deleterious sequelae.

Paroxysmal Atrial Tachycardia with Block

The relation between the potassium balance of the body and the toxic action of digitalis called attention to paroxysmal atrial tachycardia with block. This arrhythmia frequently resulted from either an absolute overdose of digitalis or a relative overdose conditioned by a changed cardiac threshold. Study corroborated and amplified the interaction of potassium and digitalis.[44]

Digitalis in toxic amounts has been reported to produce the whole gamut of cardiac arrhythmias encountered clinically.[111] Disturbances in ventricular rhythm are well recognized consequences of digitalis intoxication. Abnormal atrial mechanisms, however, are regarded as rare and nonspecific. In our experience paroxysmal atrial tachycardia with block is a

common, serious and specific clinical entity that usually results from digitalis intoxication.[112]

Electrocardiographic Features

While the presence of paroxysmal tachycardia with block can be suspected on purely clinical grounds, its identification is not possible without an electrocardiogram. It is a hybrid arrhythmia partaking of the characteristics of both atrial tachycardia and flutter. The atrial rate varies from 120 to 250, the usual rate range being between 150 and 190. The onset and offset are gradual and sequential. Unlike untreated flutter, in which 2:1 block is the rule,[113] only 30 per cent of cases of paroxysmal atrial tachycardia with block show such a response.[112] In the remainder the degree of block varies and is often inconstant. The Wenckebach type of conduction is a common finding. Consecutive PR intervals may differ significantly in duration, giving the impression on cursory examination of complete atrioventricular block. When the evolution of the arrhythmia is continuously observed a 1:1 atrioventricular response invariably precedes the emergence of the block. The impaired conduction is increased by vagal stimulation and diminished or abolished by atropine or exercise.

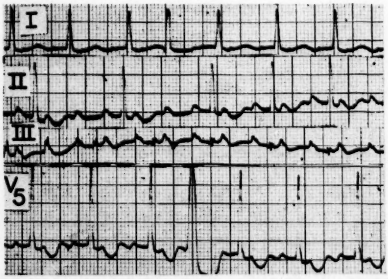

FIGURE 8. *Typical Electrocardiographic Pattern of Digitalis-Produced Episode of Paroxysmal Tachycardia with Block.*

The atrial rate is 190. Ventricular response is variable. P waves are upright in the limb leads. Note iso-electric base line in Lead 2 and ventricular premature beat in Lead V_5.

The P waves, when discernible, are upright in Leads 1, 2 and 3. They may be indistinguishable from the P waves originating in the sinus node, but generally differ in contour and amplitude. In some cases the P wave is notched or peaked and of great size. In others it is extremely diminutive, barely ruffling the base line. The PR interval may not be constant; those incorporating a QRS complex are at times of shorter duration. Unlike flutter, in which the base line is in continuous motion, in this arrhythmia an iso-electric interval separates the atrial complexes (Fig. 8).

Evidence of digitalization is usually present. The ST segment may be depressed, with inversion of the first portion of the T wave and QT-interval shortening. In addition ventricular premature beats are observed in most patients. These may occur singly or assume bigeminal patterns and at times give way to brief or prolonged runs of unidirectional or bidirectional ventricular tachycardia.

Experimental Studies

Production by digitalis. Heyl[114] was the first to demonstrate that digitalis was a causative factor of this arrhythmia. The role of digitalis and quinidine was later also suggested by Decherd, Herrmann and Schwab[115] on the basis of a study of 40 patients. Of this group, 33 had received digitalis, and in 23 the amounts were regarded as excessive by the authors. In these clinical experiences many factors were operating, and the role of digitalis was conjectural. If a relation between digitalis and paroxysmal atrial tachycardia with block exists it is necessary to demonstrate its operation without the intervention of other important variables. This was made possible by the use of acetyl strophanthidin, which permits digitalization in the course of a few minutes. To date we have observed 3 patients in whom paroxysmal atrial tachycardia with block promptly followed the intravenous administration of acetyl strophanthidin. No other drugs were utilized. The maximum interval for the emergence of the arrhythmia was twelve minutes, and its development was a gradual sequential process identical in the 3 patients.

There were roughly four phases in this development. The first consisted of an increase in atrial rate frequently associated with a slight or prominent alteration in the contour and magnitude of the P wave but not in its direction. This represented the usurpation of pace-setting function by a more excitable ectopic focus. A gradual acceleration of the atrial mechanism followed, with a continuation of a 1:1 ventricular response. The third phase consisted of migration of the P waves with increasing atrioventricular block. Lastly, when the rate had reached a critical level, 2:1 or greater or less degrees of atrioventricular block developed (Fig. 9). The critical rate at which block ensued differed from patient to patient and in any one patient under varying circumstances. The experience in these 3 patients clearly indicates the association with digitalis.

Production by potassium removal. In digitalized patients the loss of body potassium may have the same effect as the administration of additional digitalis. In the study with the artificial kidney discussed above, 7 of the digitalized patients gave evidence of intoxication during the removal of potassium by hemodialysis. In 2 of these patients paroxysmal atrial tachycardia with block developed, and in a third its maturation was stopped by potassium administration. The evo-

lution of the arrhythmia was gradual and followed the same sequence as in the patients who received acetyl strophanthidin. A change in pacemaker was the first harbinger of the tachycardia. This was followed by acceleration of rate and increasing atrioventricular-conduction impairment, which finally resulted in second degree heart block (Fig. 10). In

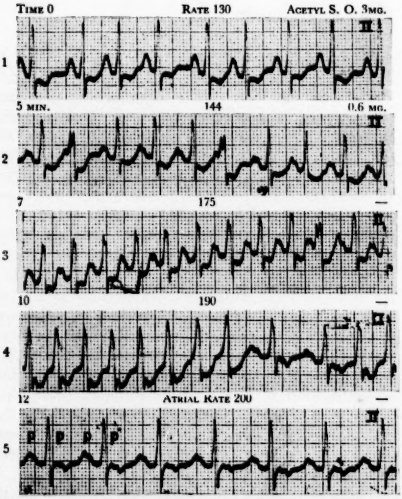

Figure 9. *Production of Paroxysmal Atrial Tachycardia with Block by the Administration of Acetyl Strophanthidin in a Digitalized Patient.*

The earliest event consists of a change in pacemaker and acceleration of rate (2). This is followed by continued increase in atrial rate and in atrioventricular-conduction time (2 and 3). At a rate of 190 both intraventricular-conduction defect and second-degree heart block become evident (3). Finally, 2:1 block becomes fully established at an atrial rate of 200 (4).

2 of the 3 patients other evidence of digitalis intoxication also developed. The reduction in the serum potassium concentration at which the arrhythmias began averaged 1 milliequiv. per liter. In all 3 patients, however, the values were above 3.5 milliequiv., and in 1 it was 5.6 milliequiv. per liter. Elevation of the serum potassium level to its value before the arrhythmia did not promptly reverse the tachycardia.

Abolition by potassium administration. When paroxysmal atrial tachycardia with block is caused by digitalis potassium is rapidly effective in restoring a normal mechanism (Fig. 11). In 10 episodes induced by digitalis in 6 patients, 20 to 100 milliequiv. (1.5 to 7.5 gm.) of potassium chloride given either orally or intravenously abolished the tachycardia (Table 4). The process of reversion of the arrhythmia by potassium was a chronologic mirror image of the stage in its evolution. The first change consisted of a slight slowing of the ectopic focus, with establishment of a 1:1 atrioventricular response. This was associated with a sudden increase in ventricular rate and with aggravation of symptoms of dyspnea and palpitation. A diminution in atrioventricular block followed, with visible migration of the P waves and continuous reduction in the heart rate. An abrupt change in the P-wave contour then resulted in the re-establishment of a sinus rhythm[44] (Fig. 11).

Potassium is ineffective in the absence of a background of digitalis intoxication. This is true even if the mechanism is paroxysmal atrial tachycardia with

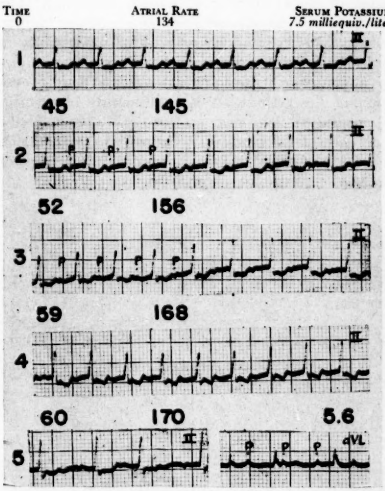

Figure 10. *Production of Paroxysmal Atrial Tachycardia with Block by the Removal of Potassium in a Digitalized Uremic Patient.*

Phases in development are similar to those when the arrhythmia is produced by an overdose of digitalis.

block. In 6 cases of atrial arrhythmias not due to digitalis, 3 of which were paroxysmal tachycardia with block, the administration of 40 to 200 milliequiv. (3.0 to 15.0 gm.) of potassium chloride did not alter the atrial mechanism. Potassium was ineffective even though hyperkalemia was produced in 3 of the 6 patients (Table 4).

It can therefore be concluded that an overdose of digitalis affects atria as well as ventricles. The atrial manifestations of advanced digitalis intoxication assume the specific form of paroxysmal tachycardia with block. The laws relating potassium to the myo-

cardial toxic threshold operate in this arrhythmia as in other cases of digitalis poisoning.

Clinical Studies

Incidence and predisposing factors. In a period of eleven years at the Peter Bent Brigham Hospital 66 episodes of paroxysmal atrial tachycardia with block were observed in 51 patients.[112] Half the episodes occurred during the past three years. In 12 of the bouts of tachycardia digitalis was not a factor. In the remainder, all of which were associated with digitalis, the evidence suggested either absolute or relative overdosage (Table 5). Of the 54 episodes 36 were due to a distinct overdose; 8 were precipitated by a massive mercurial diuresis while the patients were on maintenance digitalis therapy, and in 10 others a variety of factors involved were believed to have sensitized the patients to digitalis toxicity. In 6 of these substantial losses of potassium, resulting either from intrinsic renal lesions or from extraction by hemodialysis, were the factors. In 3 of the remaining 4 the administration of cortisone, insulin or calcium precipitated the arrhythmia, whereas in the fourth the predisposing factor appeared to be a 100-pound weight loss. Thus, in slightly over 80 per cent of the episodes, digitalis was involved in the emergence of paroxysmal atrial tachycardia with block. In all patients in whom digitalis was implicated the arrhythmia ceased when the drug was discontinued.

The data indicate a continuing increase in the observed incidence of paroxysmal atrial tachycardia with block. Although the heightened awareness and recognition of this mechanism is a factor, in all likelihood an actual rise in frequency has occurred. No doubt the conditions discussed above, at the beginning of this section, as responsible for the augmented incidence of digitalis intoxication also account for the increased incidence of tachycardia with block. An additional reason may be that potassium loss favors the development of this arrhythmia. Of the 7 patients exhibiting digitalis poisoning during hemodialysis, 2 had paroxysmal episodes and another demonstrated the early stages of the arrhythmia. In nearly half the patients, therefore, digitalis intoxication assumed the form of paroxysmal atrial tachycardia with block. In a study of electrocardiographic changes during 13 consecutive hemodialyses Kohn and Kiley[116] observed arrhythmias in 3. In 2 of these digitalis was implicated. One patient, who sustained potassium extraction, showed increasing digitalis effect and then an atrial tachycardia. In the other patient, in whom the potassium shift was small but other electrolytes, including calcium, were corrected, a brief paroxysm of ventricular tachycardia developed. This is a much higher percentage of atrial arrhythmias than

TABLE 4. *Effect of Potassium Administration on Atrial Arrhythmias.**

Cause of Arrhythmia	No. of Patients	Episodes of Arrhythmia	Type of Arrhythmia	Potassium Given	Results of Potassium Administration: Hyperkalemia	Results of Potassium Administration: Reversion of Arrhythmia
				milliequiv.	*no. of cases*	*no. of cases*
Digitalis induced	6	10	Paroxysmal atrial tachycardia with block	20-100	0	10
"Spontaneous"	6	6	Paroxysmal atrial tachycardia with block (3 cases) Flutter (2 cases) Nodal tachycardia (1 case)	40-200	3	0

*Note that potassium reverses only arrhythmias produced by digitalis.

TABLE 5. *Causes of Paroxysmal Atrial Tachycardia with Block in 66 Episodes Occurring in 51 Patients.*

Predisposing Factor	No. of Patients	No. of Episodes	Percentage of Total Episodes
Attack associated with digitalis	39	54	81.8
Overdose of digitalis		36	54.5
Mercury diuresis and digitalis maintenance		8	12.0
Miscellaneous factors and digitalis maintenance		10	15.3
Renal potassium loss		4	
Hemodialysis		2	
Cortisone administration		1	
Insulin administration		1	
Calcium administration		1	
Weight loss		1	
Idiopathic attack	12	12	18.2

would be found in a random population with digitalis intoxication. Since potassium depletion is becoming an increasing problem in patients with congestive heart failure a continuing rise in the incidence of paroxysmal atrial tachycardia with block is to be anticipated.

Prognosis. Patients in whom this arrhythmia is due to digitalis usually have serious heart disease. All 5 patients with supraventricular tachycardia studied by

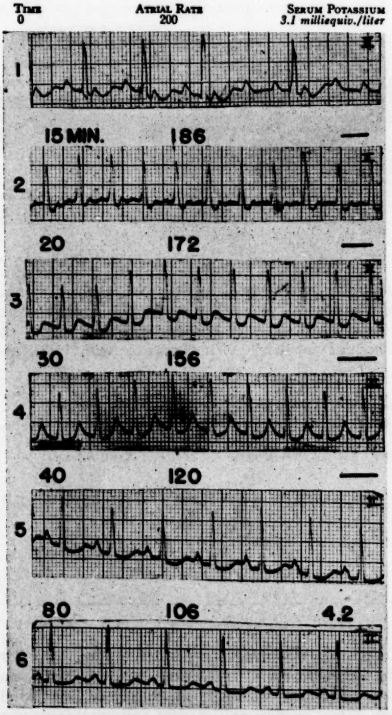

FIGURE 11. *Abolition of Paroxysmal Atrial Tachycardia with Block by the Administration of Potassium.*

The sequence of changes is the reverse of those shown in Figures 9 and 10. With slight slowing of atrial rate 1:1 atrioventricular-response phase develops, with paradoxic ventricular acceleration (2). Atrioventricular block diminishes with a decrease in atrial rate (3, 4 and 5). Finally, there is an abrupt change in the contour of the P wave with reconstitution of normal sinus rhythm.

Askey[117] died shortly after the inception of the arrhythmia. In the series of 40 patients described by Decherd, Herrmann and Schwab[118] 55 per cent died during their hospital sojourn. Of the 39 patients studied at the Peter Bent Brigham Hospital, 23 (60 per cent) died shortly after the onset of the tachycardia. Perusal of the clinical records of the Brigham patients leaves little doubt that the high mortality was related to the continued administration of digitalis, at times in increasing doses. Since paroxysmal atrial tachycardia with block is associated with ventricular rates of over 100, the tendency is to give more digitalis to slow the ventricles. In the critically ill cardiac patient this usually induces more profound toxicity and eventually death.

Idiopathic paroxysmal atrial tachycardia with block. The 12 patients in whom the arrhythmia was idiopathic differed in a number of respects from those patients in whom it was due to digitalis.[118] No etiologic agents or predisposing conditions were evident. Six of the 12 patients had not received digitalis for at least a month before the onset of the tachycardia. A digitalis effect was not present on the electrocardiogram, and only 1 patient manifested ventricular extrasystoles. Three had no demonstrable organic heart disease. The arrhythmia lasted in 6 of the 12 more than a month and in 3 for over a year. It had been present for nineteen years in 1 case and almost continuously for twenty-five years in another. In only 1 of the 39 cases due to digitalis had the paroxysmal tachycardia with block been present for longer than a month. The mortality rate was significantly lower in the idiopathic group. Two patients died (17 per cent), and in both death appeared unrelated to the auricular abnormality.

Idiopathic paroxysmal tachycardia with block is a benign condition. When it occurs in young people it is compatible with a long, healthy and active life. Digitalis therapy is not contraindicated if congestive heart failure is present. When a 1:1 response develops digitalis is the drug of choice for slowing the ventricular rate. Pronestyl, potassium or quinidine is ineffective in restoring a normal sinus mechanism.

There is another type of paroxysmal atrial tachycardia that is not related to digitalis. When atrial fibrillation or flutter is being converted to sinus rhythm with quinidine a transition phase may develop that exhibits the features of tachycardia with block. This is a transient electrocardiographic pattern devoid of clinical significance.

Differentiation from other atrial mechanisms. Paroxysmal atrial tachycardia with block may resemble nearly every atrial mechanism. Before the onset of block, when the atrial rate is slow and no previous tracings are available for comparison of P waves, it may be indistinguishable from a sinus tachycardia. When the rate exceeds 150 but the arrhythmia is still in a 1:1 response phase, it is usually considered as a supraventricular tachycardia. This is clearly demonstrated in Figure 12. The patient, whose underlying condition was a potassium-losing nephritis and malignant hypertension, had five episodes of tachycardia with block while on digitalis. The first bout (Fig. 11) was precipitated by a mercurial diuretic, and the other four by inadequate potassium supplementa-

tion. Five days after the discontinuation of digitalis, immediately after awaking and before receiving her first daily dose of potassium, she had a paroxysm of rapid heart action with a rate of 165. She appeared critically ill, with palpitation, extreme anxiety and advancing pulmonary edema. The electrocardio-

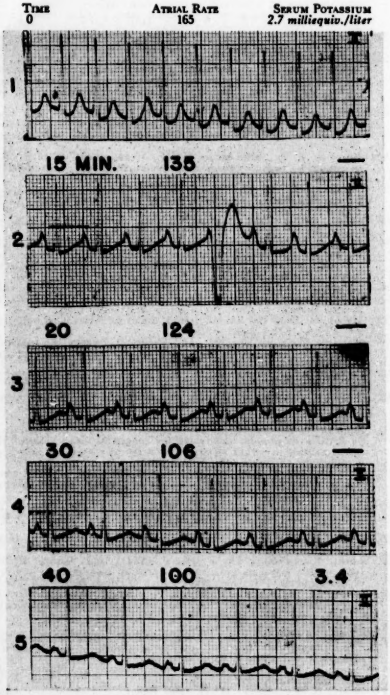

Figure 12. *Electrocardiograms in F.G.*
On the basis of the tracing (1) supraventricular tachycardia was diagnosed, and digitalis was suggested. However, the history of potassium-losing nephritis and previous episodes of paroxysmal atrial tachycardia with block suggested that this was a 1:1 response phase of the latter arrhythmia. Oral administration of potassium was effective in rapidly restoring sinus rhythm.

graphic diagnosis of her arrhythmia was supraventricular tachycardia. Since the rhythm resembled a phase in the recession of paroxysmal atrial tachycardia with block, instead of digitalis she was given 20 milliequiv. of potassium chloride orally. Within fifteen minutes her heart rate dropped to 135, and within forty minutes sinus rhythm was restored, with abatement of the signs of failure.

When the P waves are not in evidence in the standard or unipolar leads and the ventricular rate is slow because of atrioventricular block, nodal rhythm is the likely diagnosis. Patient C. W. represents such a case of electrocardiographic misinterpretation (Fig. 13). This sixty-six-year-old man with rheumatic mitral and aortic disease had had atrial fibrillation for eleven years. For more than a year the ventricular rhythm had been perfectly regular on auscultation. The electrocardiogram during this time was interpreted as showing nodal rhythm. However, the application of carotid-sinus pressure, while a precordial lead was maintained in the V_1 position, revealed the true nature of the arrhythmia.

Atypical flutter is another name used by some for paroxysmal atrial tachycardia with block. This is a misnomer, for it implies that the two mechanisms are nearly identical expressions of a common underlying

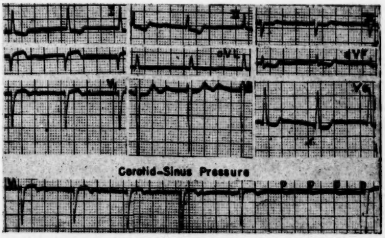

Figure 13. *Electrocardiograms in C.W.*
For over a year the rhythm appeared regular on auscultation, and electrocardiograms were interpreted as showing nodal rhythm. The perfectly iso-electric base line in all leads raised suspicion, however, of the underlying mechanism. When carotid-sinus pressure was applied while a V lead was being taken the presence of paroxysmal atrial tachycardia with block was revealed.

process.[45] Aside from important differences in pathogenesis and treatment there are significant electrocardiographic and clinical differences. The patient in whom flutter develops is on the average a decade older than the one with tachycardia with block. He is less likely to have severe heart failure. He has not been on rigid salt restriction and has not received frequent mercurial injections before the onset of the rapid heart action. In flutter the atrial rate exceeds 250; in paroxysmal atrial tachycardia with block it is invariably less. The following electrocardiographic features further differentiate the two arrhythmias: in untreated flutter, atrioventricular block is usually 2:1; the Wenckebach type of conduction is rare; in nearly 70 per cent of the cases the P waves are inverted in Leads 2 and 3[45]; the base line between P waves is not iso-electric but has an undulant, sometimes see-saw quality; and ventricular premature beats are rare. The prognosis in flutter is more favorable and is about the same as that in the idiopathic variety of tachycardia with block.

Paroxysmal atrial tachycardia with block is at times confused with atrial fibrillation. The diminutive P waves and changing degrees of atrioventricular block conduce to misinterpretation. The development of tachycardia with block is not precluded by many years of chronic fibrillation. Some of the cases of atrial fibrillation reported in the literature after digitalis overdosage may have been examples of paroxysmal atrial tachycardia with block.

When the ventricular rate of a patient with long-standing fibrillation accelerates and regularizes after a diuresis or an increased dose of digitalis, tachycardia with block should be suspected. When the routine leads do not show this mechanism, exploration of the precordium with CR leads may demonstrate the blocked P waves. Mild exercise may be helpful diagnostically. In the presence of fibrillation the irregularity will be increased; the converse is true in paroxysmal atrial tachycardia with block. Carotid-sinus pressure may prove rewarding: it frequently enhances atrioventricular block, revealing the presence of nonconducted P waves. Nevertheless, a significant number of cases remain in which identification of the mechanism is difficult. In such patients a test dose of potassium or a digitalis tolerance test may identify the arrhythmia.

(To be concluded)

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MEDICAL INTELLIGENCE

AN UNUSUAL CASE OF SPOROTRICHOSIS

MAURICE L. SIEVERS, M.D.*

BRIGHTON, MASSACHUSETTS

SPOROTRICHOSIS is a chronic fungous infection caused by *Sporotrichum schenckii*. Characteristically, nodular lesions appear in the lymphatic channels, skin or subcutaneous tissue and later break down to form indolent ulcers, referred to as sporotrichotic chancres. The organism exists parasitically on many plants and timbers and is infectious for many animals, including man.[1,2] The usual portal of entry in man is at a site of trauma to the skin. Initial lesions appear from twenty days to three months after inoculation.[1] Although some difference of opinion persists[3] most American authors agree that there is only one species of sporotrichum responsible for human sporotrichosis.

Since sporotrichosis was first reported in a St. Louis iron worker by Schenck in 1898 the condition has been described in all countries. In the United States the greatest incidence has been in the Mississippi valley. However, the relative infrequency of sporotrichosis in this country is shown by the fact that, through 1951, only 275 cases had been reported.[4] This contrasts with a report of 2825 cases from the gold mines of South Africa between 1941 and 1944.[5] Only eight cases of this disease have been reported from the New England area. Of these, 4 were from Connecticut,[6-8] 2 from Massachusetts[9,10] and 1 each from Maine[11] and New Hampshire.[12]

The case reported below is of interest because of the unusual manner in which the disease was probably acquired. It also presents the detailed observations of development and subsequent cure of the disease. Although sporotrichosis was contracted in Massachusetts, in this case, there is a definite possibility that the immediate source of infection originated in another geographic area.

CASE REPORT

C. F. (U.S.P.H.S.H. 67502), a 36-year-old male post-office clerk, was referred to the Outpatient Department of the United States Public Health Service Hospital by the post-office nurse on May 1, 1953, because of a small, erythematous, nontender, swollen area on the lateral aspect of the knuckle of the left index finger. The patient stated that this area had been penetrated 7 days earlier by a small splinter from a wooden carton, which he had handled in his duties at the post office. The mailing site of the box could not be remembered or determined in retrospect. One week later he noted a small, red area around the site of injury and reported to the post-office nurse, who perforated the area with a sterile hypodermic needle in an unsuccessful search for a splinter and then referred him to this hospital.

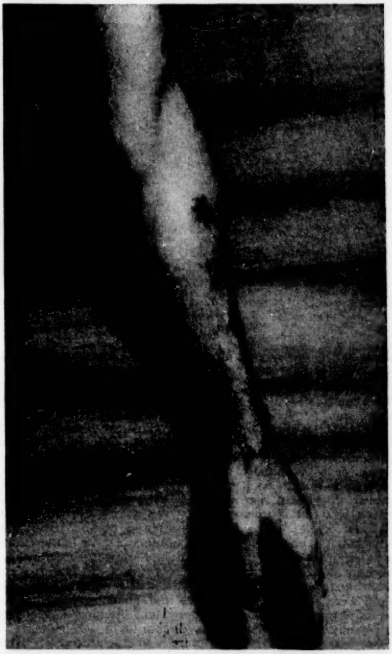

FIGURE 1. *Nodules along the Pathway of the Lymphatic Channel Draining the Original Sporotrichotic Lesion of the Index Finger.*

The prominent linear lesion below the antecubital area is a sinus tract at a biopsy site.

Examination showed slight erythema and edema surrounding a pin-sized puncture wound on the lateral aspect of the left index finger near the proximal crease (the distal phalanx had been traumatically amputated several years previously). The patient was afebrile and without systemic symptoms. There was no evidence of lymphadenopathy or lymphangitis. Procaine penicillin, 600,000 units, was administered intramuscularly, and 0.5 cc. of tetanus toxoid given. He was instructed to begin periodic hot saline soaks.

Five days later a small amount of thin, purulent discharge from a persistent sinus tract of the left index finger was noted. To promote drainage the opening was surgically enlarged. Twenty-one days after the initial wound, 3 firm, movable, nontender, subcutaneous nodules along the lateral aspect of the left wrist were observed to be developing in approximately a linear pattern (Fig. 1). Each of these was from 5 to 7 mm. in diameter and without discoloration.

*Senior assistant surgeon, United States Public Health Service; third-year resident in internal medicine, Public Health Service Hospital.

The patient was not seen again until 19 days later, when several similar nodules were noted extending along a winding pathway up the lateral aspect of the left forearm and arm to near the axilla. The sinus tract of the left index finger persisted, with a thin, purulent discharge; surrounding this were 6 to 8 small, flat, verrucous, satellite lesions (Fig. 2). A cord-like connecting structure between the nodules, more pronounced near the lower chronologically older lesions, was felt. He had remained afebrile and without systemic symptoms. X-ray examination of the left hand showed no bony disease or evidence of foreign body. The

FIGURE 2. *Sporotrichotic Ulcer on the Index Finger Surrounded by Verrucous Satellite Lesions.*

white-cell count was 5000, with 65 per cent neutrophils, 29 per cent lymphocytes, 2 per cent monocytes and 4 per cent eosinophils. The hemoglobin was 15.5 gm. per 100 cc., and the hematocrit 45 per cent. Erythrocyte sedimentation rate was 8 mm. per hour (Wintrobe method, corrected).

The patient was admitted to the Surgical Service on June 8, with the diagnosis of possible mycotic infection. Careful questioning failed to elicit any history of contact with domestic or wild animals.

Physical examination showed an afebrile man who did not appear ill. There was no significant lymphadenopathy, the spleen was not felt, and there were no noteworthy abnormalities besides those previously noted in the left upper extremity. A chain of 12 to 15 nontender and nonfluctuant nodules, from 3 to 10 mm. in diameter, were observed extending along the radial aspect of the left forearm and the flexor surface of the arm into the axilla. The lower 5 of these were slightly erythematous and fixed to the skin, but the others were freely movable and not discolored. None of these showed any ulceration or discharge.

At this time the blood picture was unchanged. A serologic test for syphilis was negative. Serum agglutination tests for brucella and tularemia were negative. Urinalysis revealed a specific gravity of 1.030; tests for albumin and sugar were negative. On microscopical examination of 3 separate urine specimens, from 15 to 25 red blood cells per high-power field were noted in the uncentrifuged sediment, but there were no other cellular or formed elements. Cultures of 2d-glass voided specimens and of urine obtained at cystoscopy as separate specimens from the bladder and from each ureter were all negative by appropriate culture methods for micro-organisms, including tubercle bacilli and fungi. An intravenous pyelogram with iodopyracet revealed only minimal hydronephrosis on the right; this was confirmed without additional findings by retrograde pyelography. Numerous subsequent urinalyses showed no further microscopical hematuria.

Bacteriologic culture of exudate from the sinus tract on the left finger grew only hemolytic staphylococci; culture of this material on Sabouraud agar medium was productive of numerous colonies, all of which were miscroscopically identified as *S. schenckii* (Fig. 3). X-ray examination of the chest revealed no significant abnormality. A Vollmer patch test for tuberculosis was positive.

On June 12, 2 of the erythematous, fixed nodules on the lower left forearm were excised for biopsy. Grossly, they appeared to be an intimate part of the subcutaneous fatty tissue. Microscopical examination demonstrated intense focal infiltration of fibroadipose tissue with lymphocytes, plasma cells and occasional mast cells and eosinophils. Proliferating fibroblasts and scattered histocytes were also seen.

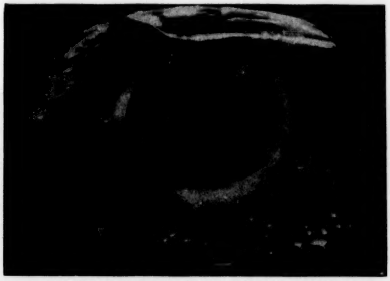

FIGURE 3. *Gross Appearance of a Colony of* Sporotrichum schenckii *Cultured on Sabouraud's Agar.*

No micro-organisms were present. The pathological interpretation was granulomatous inflammation of the subcutaneous tissue.

Bacteriologic culture of the biopsy specimen revealed no growth. Culture on Sabouraud agar was productive of a growth of 4 colonies. On the 6th day of incubation microscopical examination of these colonies revealed branching mycelia with aerial mycelia-bearing conidia (Fig. 4). These were considered morphologically typical of *S. schenckii* in

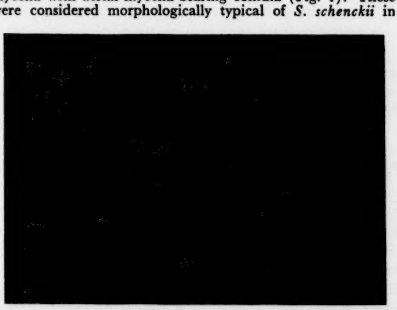

FIGURE 4. *Photomicrograph* of Sporotrichum schenckii *Isolated from the Patient, Showing Aerial Mycelia-Bearing Conidia, Resembling Clusters of Pine Cones (X 480).*

pure culture. Subsequently, this identification was confirmed by the report on a colony submitted to the United States Public Health Service Communicable Disease Center in Chamblee, Georgia.

On June 19 therapy was instituted with potassium iodide solution 3 times a day, beginning with 10 drops and increasing each dose by 5 drops until a dosage of 45 drops 3 times a day was reached and thereafter continued. By the 6th day all drainage had ceased from both the sinus tract at the site of original injury and from a sinus tract that had formed at the biopsy site. Within 4 weeks of the institution of treatment none of the nodular lesions could be palpated, the sinus tracts had disappeared and the satellite verrucous lesions on the left index finger were gone. A few acneform lesions appeared on the skin of the face and chest during the 3d week of treatment. This was considered to be an iodide reaction, and the dosage of potassium iodide solution was decreased to 25 drops 3 times a day, with gradual improvement and eventual clearing of the eruption.

Treatment was continued for 3 months. The patient was entirely asymptomatic and without clinical evidence of

sporotrichosis when seen for follow-up study 4 months after the initiation of treatment.

Discussion

In this country the most frequent type of sporotrichosis is the localized lymphatic form.[1] Typically, an erythematous area first appears on an extremity at the portal of entry, with later ulceration and chronic drainage of purulent material. This is followed by the progressive development of nontender, nodular lesions along the draining lymph channel. Systemic symptoms are uniformly absent. A disseminated subcutaneous form may be the result of blood-stream spread. Sporotrichosis may also involve the mucous membranes, skin,[13] skeletal system or various viscera. In striking contrast to the other mycoses, however, the lungs are rarely a primary site.[1]

Because of the frequency of a botanical source of infection horticulturists in this country appear to be one of the most susceptible groups.[14] Direct human transmission from one person to another has not been reported.[1] Prognosis for recovery with the localized lymphatic form of sporotrichosis is usually excellent. In the 206 cases reported in the literature before 1941 there were only 5 deaths.[14] Iodides are almost a specific therapeutic agent, and the results are better in sporotrichosis than in any other fungous disease.[1] There have been only 8 reported cases of unsatisfactory response to iodide therapy.[15] Ancillary agents that may also exert some beneficial effect include irradiation, autogenous vaccine and fever therapy.[16] Penicillin,[17] streptomycin,[17] chlortetracycline and chloramphenicol[18] are usually without effect, although an occasional case shows some response to sulfonamides.[2] Clinical experience with stilbamidine in sporotrichosis is limited, but a case of successful treatment of the lymphatic form of the disease with this drug was recently reported.[19] However, because of the severe toxic reactions that stilbamidine may provoke, it seems advisable to utilize it only in cases unresponsive to iodides or in others in which the risk seems warranted on clinical grounds. The disease may persist many months or years if untreated.

Diagnosis in most cases is fairly clear from the typical clinical picture, particularly in the localized, lymphatic form. Ready confirmation is obtained by cultures of discharging material, aspirated pus or a portion of a biopsy specimen, with Sabouraud's medium. Disadvantages to routine biopsy procedures include the fact that, unlike all other fungous infections of man, the organism is almost never seen in the microscopical examination of the granulomatous lesion,[1] and, furthermore, there is a distinct tendency for prolonged discharge of pus from the biopsy site. A confirmatory skin test and serologic tests are also available. Inoculation of susceptible animals may be employed. Among the diseases to be considered in differential diagnosis are tularemia, brucellosis, syphilis, tuberculosis, glanders, pyogenic infections, leishmaniasis, granulomas due to drugs, blastomycosis and other deep mycoses.[4]

Summary

A typical case of lymphatic sporotrichosis in a postal employee is presented. Although the infection was acquired in Massachusetts, there is a distinct possibility that the organism originated in another part of the country and was transported through the mail on a wooden carton. General pertinent factors in this type of infection are discussed.

I am indebted to Dr. Robert C. Rodger, pathologist, United States Public Health Service Hospital, Boston, for his pathological interpretations and for suggestions in the preparation of this paper.

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LATE REACTION TO HYDRALAZINE (APRESOLINE) THERAPY

Wilbur B. Manter, M.D.*

BANGOR, MAINE

THERE have been few reports on late reactions to hydralazine (Apresoline) therapy. Attention was recently called to a syndrome resembling acute systemic lupus erythematosus associated with prolonged treatment of hypertension with large doses of hydralazine.[1] Two reports[2,3] have appeared describing a syndrome resembling early rheumatoid arthritis or disseminated lupus erythematosus occurring in 13 of

*Attending physician, Eastern Maine General Hospital.

139 and 14 of 253 patients whose treatment included hydralazine. It is of particular interest that all the patients with this syndrome had received relatively large doses of the drug for at least three months. Remission followed the cessation of the drug, usually within a few days. ACTH and cortisone suppressed the condition. Positive L.E. tests were found in several patients.

Case Report

A 28-year-old man was admitted to the Eastern Maine General Hospital on October 31, 1953. For the previous month he had malaise, an intermittent fever to 101°F., sweats at night and migratory aching in the joints of the extremities. At times, lameness had been sufficiently severe so that he had had to crawl upstairs at night. In the morning, the fingers felt swollen and were stiff so that opening the hands was difficult. There had been a 10-pound weight loss.

For the previous 9 months, he had taken hydralazine, 150 mg. 4 times daily. Except for omitting it 1 day at about the end of the 2d week of this illness, he had continued to take it regularly. On the day after he omitted the drug the symptoms were greatly lessened. Salicylates had given incomplete relief.

He had first learned of his hypertension at the age of 18, when he was rejected for induction for military service. In February, 1949, the blood pressure had ranged between 180/118 and 218/135. In the following April, after appropriate study at the Smithwick Foundation, a bilateral splanchnicectomy was performed. Since he was planning marriage and wished to have no interference with his sexual function, the operation was carried down through the 12th dorsal segment only on both sides. From February, 1950, to April, 1953, he followed a low-sodium diet (200 mg.) conscientiously. From October, 1950, to some time early in 1952 he had received several preparations of *Veratrum viride*. No sustained significant reduction in blood pressure occurred during this time.

In December, 1952, he was admitted to the Eastern Maine General Hospital with retinal hemorrhages in the right eye. The heart did not appear enlarged on x-ray examination, and an electrocardiogram was normal. Kidney function was good, with a negative urinalysis. Examination of the blood showed a red-cell count of 5,090,000, with a hemoglobin of 17.5 gm. per 100 cc., and a white-cell count of 6000. The platelets appeared normal in the smear. At rest in the hospital daytime diastolic pressures ranged between 110 and 145, dropping to between 90 and 100 with sedation and sleep at night. Hydralazine was started in the hospital. After discharge the dose was gradually increased to 150 mg. 4 times daily, the systolic blood pressure remaining between 130 and 150 and the diastolic close to 90. In June, 1953, the ophthalmologist who had previously observed the retinal hemorrhages and had classified the fundi as Class 3 hypertensive considered the retinal examination negative. The low-sodium diet was discontinued at this time. Subsequently, the blood pressure remained unchanged.

On admission to the hospital physical examination was remarkable only for an appearance of fatigue and for swelling and tenderness at the proximal interphalangeal joint of the 2d left finger. The blood pressure was 140/85. Examination of the blood demonstrated a red-cell count of 4,190,000, with a hemoglobin of 11.5 gm. per 100 cc., and a white-cell count of 3500, with 62 per cent neutrophils, 4 per cent band forms, 31 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils. The sedimentation rate was slightly elevated. The urine had a specific gravity of 1.022, with an albumin of 0.05 per cent, and 25 to 50 red cells per high-power field in the sediment. Agglutinations for the common febrile antigens and for heterophil antibodies were negative. The nonprotein nitrogen was 32 mg. per 100 cc. An electrocardiogram was normal. A chest film was interpreted as showing a smaller heart, with less prominence of the aorta, as compared with the examination in December, 1952. Bleeding and clotting times and capillary fragility were normal. On the 3d hospital day the patient could raise small amounts of mucoid sputum, which was slightly streaked with red blood.

On the 2d day after hydralazine had been omitted he felt better, and all joint symptoms had disappeared. The blood pressure was 170/120.

Several weeks after discharge from the hospital an abstract[1] referring to a syndrome resembling acute systemic lupus erythematosus associated with hydralazine therapy was found. Consequently a plasma L. E. preparation was made 4 weeks after the omission of hydralazine, and L. E. cells were present. A 2d preparation 2 weeks later was negative. Examination of the blood at this time showed a red-cell count of 3,700,000, with a hemoglobin of 12.0 gm. per 100 cc., and a white-cell count of 4700, with 59 per cent neutrophils, 2 per cent band forms, 3 per cent metamyelocytes, 28 per cent lymphocytes, 1 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils.

The patient has continued to be well and has regained the 10 pounds of weight that had been lost. Other hypotensive agents, including *Rauwolfia serpentina* and a protoveratrine preparation, had been started shortly after discharge from the hospital. Because of interfering circumstances the tolerance dose of the protoveratrine drug has not yet been reached. On January 6, 1954, the blood pressure was 165/140 after a 15-minute rest period. Examination of the blood revealed a hemoglobin of 13.5 gm. per 100 cc., a white-cell count of 6000, with 40 per cent neutrophils, 8 per cent band forms, 1 per cent metamyelocytes, 48 per cent lymphocytes, 1 per cent monocytes and 2 per cent eosinophils. The sedimentation rate remained slightly elevated and urinalysis showed an albumin of 0.01 per cent, with 1 to 3 hyaline casts per low-power field and 10 to 20 red cells per high-power field.

Discussion

After apparent control of hypertensive disease in a young man for nine months, it was distressing to have the therapeutic weapon backfire. The patient's condition is about back to where it was before hydralazine was started, when almost three years of strenuous therapeutic efforts, including major surgery with a prolonged convalescence, a very unpalatable diet that precluded entering into many of the everyday social activities and various drugs, had been of no avail. In addition to the problems of the hypertension there now seems to be some uncertainty still about the future course of this syndrome, which resembles a collagen disease.

Summary

After nine months of hydralazine therapy, 600 mg. daily, a syndrome including malaise, low-grade fever, weight loss and migratory arthralgia developed. Mild anemia with leukopenia, elevation of blood sedimentation rate, hematuria and plasma L. E. cells were demonstrated. The symptoms were relieved a few days after hydralazine had been stopped. After two months the patient was well and had regained the lost weight, and the anemia had improved without specific treatment.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40191

PRESENTATION OF CASE

First admission. A forty-eight-year-old longshoreman entered the hospital because of hemoptysis.

Seven months earlier he had been admitted to another hospital because of black stools and weakness. A duodenal ulcer was reported on radiologic examination. He was discharged on Gelusil, a bland diet, liver and iron, with subsequent return of strength and apparent cessation of bleeding. Two months before admission he began to notice blood-streaked sputum. His physician told him that he was probably bleeding from his gums. However, the hemoptysis persisted and seemed to be aggravated by cold weather and coughing. He had associated malaise and fatigability but denied any weight loss, anorexia or pain.

He had been in good health until the present illness. There were no signs or symptoms of a bleeding tendency in the past.

Physical examination revealed a well developed and well nourished man in no apparent distress. Nothing abnormal was found. The lungs were clear.

The temperature was 97.6°F., the pulse 96, and the respirations 20. The blood pressure was 120 systolic, 90 diastolic.

Urinalysis showed a specific gravity of 1.028, an acid reaction and a normal sediment. Examination of the blood disclosed a hemoglobin of 13.5 gm. per 100 cc., a white-cell count of 8900, with 66 per cent neutrophils, a sedimentation rate of 20 mm. per hour, a bleeding time of five and a half minutes, a clotting time of seven minutes, normal capillary fragility and a prothrombin time of 14 seconds (normal, 13 seconds) (70 per cent of normal). The nonprotein nitrogen was 35 mg., and the total protein 6.9 gm. per 100 cc. A blood smear revealed normal red cells and adequate platelets. A tuberculin test (purified protein derivative) was positive in second strength. Smears of sputum demonstrated fusiform bacilli and spirochetes but no acid-fast bacilli. Throat cultures were negative for pathogens. An x-ray film of the chest was reported as showing prominent bronchovascular markings of both upper lobes but no active disease. Films of the sinuses were normal.

An ear, nose and throat consultant pointed out chronic nasopharyngitis and chronic rhinitis but found no definite cause for the bleeding. On bronchoscopic examination fresh blood was encountered in the left main-stem bronchus, but this was thought to be from instrumentation. The remainder of the tracheobronchial tree was normal. A smear and washings were taken from the left main-stem bronchus. Cytologic studies on these were recorded as doubtful. Cytologic examinations of the sputum were negative. Repeated chest films were reported as showing multiple, poorly defined densities throughout both lung fields, with an area in the right-midlung field that suggested cavitation with a fluid level. There was no evidence of mediastinal abnormality.

The patient was discharged on the third hospital day to be followed in the Out Patient Department.

Final admission (three weeks later). While he was being seen in the clinic skin tests with coccidioidin and histoplasmin were read as negative in forty-eight hours. The Widal reaction and agglutination tests for *Brucella abortus* were negative. A gastrointestinal series was reported to be normal. One week before admission he was started on penicillin and sulfadiazine. Two days later he noted marked increase in the hemoptysis, with progressive fatigability and shortness of breath. Two days before admission he fainted while eating. When he revived he was sweating profusely and was extremely dyspneic. He was taken to another hospital, where he was found to have a hemoglobin of 50 per cent (Sahli) and a white-cell count of 14,000, a tender abdomen and x-ray evidence of consolidation in the right middle and lower lobes. He was given oxygen, opiates and two blood transfusions, with some improvement in the symptoms. Two days later he was transferred to this hospital.

On physical examination he appeared acutely ill. The left lung was clear to auscultation and percussion. In the right lung there were dullness and diminished to absent breath sounds over all but the apical portions. The epigastrium was nontender but exhibited some spasm.

The temperature was 101°F., the pulse 120, and the respirations 36. The blood pressure was 102 systolic, 56 diastolic.

The hemoglobin was 10.2 gm. per 100 cc., and the white-cell count 11,750. An x-ray film of the chest showed multiple, ill defined densities in both lung fields and considerable fluid in the right pleural space.

Later the same day the blood pressure fell suddenly to 42 systolic, 0 diastolic; the pulse rose to 140, and

dyspnea became more severe. The neck veins were distended. Venous pressure was equivalent to 150 mm. of water. There was a pulsus paradoxicus (pressure equivalent to 10 mm. of mercury). The heart sounds were not unusual, and no friction rub was heard. An electrocardiogram was normal. The hemoglobin dropped to 7.0 gm. per 100 cc., and the temperature rose to 103°F. Plasma and blood, as well as oxygen, were given. Daily administration of penicillin was started. A roentgenogram of the chest taken the next day showed a marked increase in the pleural fluid on the right (Fig. 1). On the second hospital day 1550 cc. of bloody fluid was removed from the right side of the chest by thoracentesis. This fluid had a hematocrit of 14 per cent and a white-cell count of 7000 per cubic millimeter. The next day the patient again had a severe episode of dyspnea. The hematocrit was 27 per cent. He was given 2000 cc. of whole blood, and the chest was tapped again, yielding 550 cc. of bloody fluid. During the next several days these episodes of severe dyspnea recurred, and transfusions were given according to the hematocrit level. Several thoracenteses yielded approximately 200 cc. of bloody fluid each time. An attempt at thoracoscopy was unsuccessful. The temperature ranged between 100 and 103°F. A chest film on the tenth hospital day showed some increase in the size of the ill defined densities scattered throughout the lungs. At this time the hematocrit seemed stabilized, and he was subjectively improved, although he continued to cough up blood. On the eleventh hospital day severe dyspnea, with grunting respirations, again developed, and he was ashen in color but not cyanotic. A roentgenogram revealed a marked increase in fluid, which practically filled the right pleural cavity (Fig. 1). His dyspnea progressed until he died the next afternoon, the twelfth hospital day.

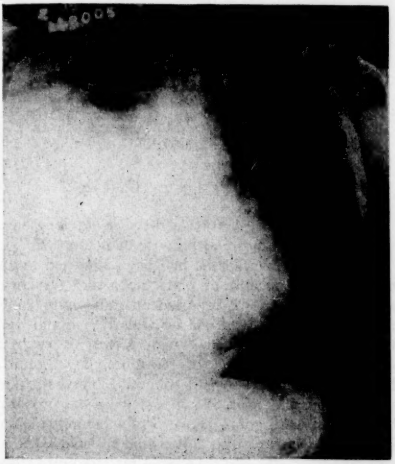

FIGURE 1.

DIFFERENTIAL DIAGNOSIS

DR. JOHN W. CASS*: May we see the x-ray films?

DR. C. C. WANG: The examination of the chest shows generalized accentuation of the pulmonary markings on both sides. I should disagree somewhat with the interpretation of the first films recorded in the protocol; I think there is active disease, some increase in pulmonary markings and an area of ring-like density between the upper and middle lobes overlying the minor fissure. This finding is confirmed by the examination two days later. In addition we see multiple ill defined densities throughout both lung fields. Approximately ten days later these mottled densities have increased in size and in number throughout both lung fields, and two weeks after the third examination, there are striking changes in both lung fields, with fluid in the right pleural space and a further increase in size and number of the mottled increased densities. One day later there is obviously a sudden increase in density in the right pleural space, indicating a hemorrhage into the right pleural cavity. During the hospital course the patient had multiple examinations; in the films made two days after the onset of hemorrhage into the right pleural cavity, there is further exaggeration of all the mottled densities throughout both lung fields. On the grid film there appears to be a large area of soft-tissue density suggesting a mass in the right-midlung field. All these findings progressed until the patient died. The gastrointestinal series is negative; no ulcer is seen.

DR. EDWARD F. BLAND: Would you comment on the heart? Is that normal?

DR. WANG: I forgot to mention the peculiar density around the right border of the heart, which was not seen on the first examination. The cardiac shadow otherwise is not remarkable.

DR. CASS: This history started with the episode of gastrointestinal bleeding several months before the first admission for hemoptysis, which raises the question of whether the two situations were related. There was no evidence that the patient had any disturbance of the blood that would cause bleeding — he had a normal clotting time, a normal bleeding time and enough platelets. I believe it is safe to detach the first episode of gastrointestinal bleeding from the sub-

*Assistant physician, Massachusetts General Hospital.

sequent course of the disease and state that there was no evidence of a blood dyscrasia compatible with a bleeding tendency.

The amount of blood raised from the chest and the apparent hemorrhage into the pleural space are certainly unusual. Massive bleeding into the pleural space is usually associated with some sort of trauma rather than with intrinsic pulmonary disease; massive intrapulmonary bleeding is usually associated with erosion of a vessel by a primary carcinoma, tuberculosis or some other condition that erodes blood vessels. Metastatic lesions bleed but usually not in massive quantities. Those that I have seen have been from unusual types of tumors; recently, I have seen a great deal of bleeding from metastasis from a seminoma. Infarcts bleed but not massively. Moreover, it would be unusual for them to cause massive hemorrhage into the pleural space. The x-ray films do not suggest infarcts. There was nothing in the history or physical examination to make me believe that the leg veins were a source of emboli. There is no evidence that the patient had tuberculosis — the x-ray films do not suggest tuberculosis; the sputum was examined several times and showed no acid-fast organisms. There was no history of trauma that would account for the sudden hemorrhage into the pleural space.

There was scant information about that sputum; I do not know its type or quantity or whether it was cultured. There was one statement that several smears of the sputum contained fusiform bacilli and spirochetes. If this was true it has to be given consideration. Vincent's type of infection of the lungs is rare, but when it occurs it is particularly difficult to handle. This man was given penicillin by his physician and apparently had a reaction to it: the blood raised became more abundant, the cough was aggravated, and there was marked deterioration of the clinical picture. An exacerbation of a pulmonary fungous infection sometimes occurs in patients who are given penicillin. A Vincent type of infection, however, should be helped by penicillin.

The pleural fluid was bloody from the time of admission. There was no information that tumor cells were found in the pleural fluid. If metastatic disease involving the pleura resulted in this amount of blood, tumor cells should have been easily found. I suspect that the patient had relatively little pleural disease and that the blood was from the pulmonary disease itself. If the process was infectious, culture of the fluid probably would have been positive.

Bronchoscopic study was apparently of no help. It ruled out primary neoplasm as far as the instrument could be passed but not a lesion beyond the scope of the instrument. Of course, metastatic disease can seldom be seen bronchoscopically. The examination of the pleural space directly was reported as unsuccessful, though one might have obtained some information merely by putting the instrument through the chest wall. Often, the operator has the distinct impression that he is going through relatively thick gritty tumor tissue. The evidence indicates that there was not much pleural disease. The x-ray films show an extremely rapid advance of the lesion and tend to make me believe that this was not a neoplastic process. The question of a mass is somewhat against this, and the shelling out of the area noted in subsequent films may simply have been one of the primary foci of the disease.

I cannot make a diagnosis of any blood dyscrasia that would cause bleeding or of tuberculosis. As far as I know, the skin test rules out coccidioidomycosis and histoplasmosis. If this was a neoplasm it was an atypical metastatic disease. The patient did not have the clinical history for adenomatosis or alveolar-cell carcinoma. Several smears were positive for the Vincent type of infection, but there was no other evidence for infection. Moreover, I should expect the diagnosis to have been made if the pleural fluid had been cultured and examined for tumor cells. The widespread process in the chest is compatible with an infectious disease. The penicillin that he was given might have helped the situation if there had been a Vincent type of infection but not if there had been a more uncommon type of infection, like a fungus. A Friedländer bacillus would not have been influenced by this type of therapy. I suspect that this was an infectious process of an uncommon type, such as one due to a Vincent or a Friedländer organism or a fungus.

DR. BLAND: On the ward we considered the various conditions that Dr. Cass has mentioned; we even wondered in the beginning, when most of the bleeding was in the air passages, whether we were overlooking mitral stenosis. We have seen patients who raised 500 to 700 cc. of blood repeatedly with mitral stenosis — in rare cases even to exsanguination. However, I cannot visualize how bleeding into the pleural cavity could result from mitral stenosis, and also we could find no evidence of heart disease in this patient. The second possibility that we seriously considered at the outset was multiple pulmonary infarcts. There was no evidence that the heart was strained through the progressive disease; cor pulmonale did not develop, and I have never seen a patient bleed intrapleurally to that extent with a pulmonary infarction. In any event one therapeutic measure was impossible — namely, anticoagulants; the other possibility would have been venous ligation, which we decided against. We did not know exactly what was behind this rapidly progressive illness, but we favored as the most likely diagnosis a very active tumor in the lung, bilaterally located, rather than infarction.

DR. YANG WANG: I should like to make a correction in the history: the patient started to have hemoptysis six months rather than two months before admission and was being followed in the outpatient clinic, nobody being quite sure what he had. There was considerable discussion about the initial x-ray

films; only one member of the Department of Radiology was convinced that they showed anything. It was quite apparent that there was bleeding both internal and external to the lung. Dr. Stokes raised the question of necrotizing arteriolitis as recently described by Fienberg.* There seemed to be little that we could do except to try to keep ahead of the game by transfusions, oxygen and sedation. We thought that there was widespread neoplastic disease in the lungs and did not consider pulmonary infarcts or infection very seriously as the main process.

DR. HELEN S. PITTMAN: This case was discussed at great length at pulmonary rounds. I said I had seen a patient with massive bleeding into the pleural space, who at autopsy had multiple pulmonary infarcts. Dr. Edward D. Churchill recalled a patient who had been sent to him with the diagnosis of metastatic disease with multiple round lesions in the x-ray films that were subsequently proved to be infarcts. Dr. Bland said he did not think anything bled both into the pleural cavity and from the mouth except cancer.

DR. CASS: I have never seen infarcts act like this, but I have seen a patient who had multiple areas throughout the lung that simulated infarction and who did bleed both by mouth and into the pleural space. At autopsy there were necrotic areas in the lung and an aplastic type of bone marrow, and that was all. Apparently, he had a reaction to one of the sulfonamides.

DR. JOSEPH STOKES: Thoracoscopic examination was planned, but the instrument was never actually introduced into the thorax because the surgeon was unable to establish an adequate pneumothorax.

CLINICAL DIAGNOSES

Carcinomatosis of lungs.
?Pulmonary infarcts.
Hemothorax, right.

DR. JOHN W. CASS'S DIAGNOSIS

Pulmonary infection due to Vincent's, Friedländer's or fungous organism.

ANATOMICAL DIAGNOSES

Hemangiosarcoma involving lungs, pleura, pericardium, myocardium and mediastinum.
Hemothorax.
Hemopericardium.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: At autopsy we found 1800 cc. of blood and blood clot in the right side of the chest and 200 cc. in the left. When the blood was removed, in the cardiophrenic angle adherent to the right ventricle of the heart was a large hemorrhagic necrotic mass that we thought was either tumor or organized blood clot. The pleural surfaces of both lungs were studded with nodules that suggested tumor on gross inspection. These nodules were quite hemorrhagic and when sectioned contained necrotic hemorrhagic centers. Many similar hemorrhagic nodules, varying in size from 3 mm. to 2 cm., were scattered throughout the lung parenchyma. In the gross they reminded some of us of the hemorrhagic metastases that are seen with a choriocarcinoma. These nodules were found in the pleura, in the lung, attached to the pericardium invading the heart muscle and in the posterior mediastinal tissue attached to the aortic wall. There were no other nodules elsewhere. We were unable to find a primary tumor in any of the bronchi or in any other organ of the body.

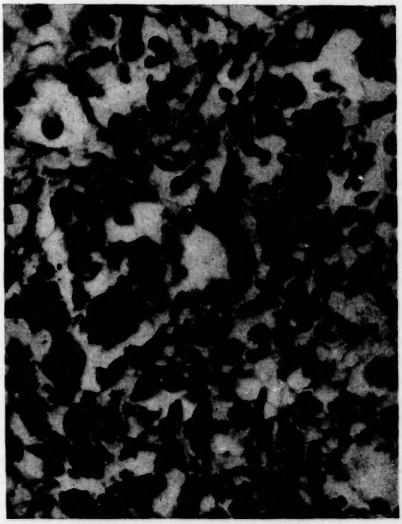

FIGURE 2.

Microscopical examination showed that these nodules were neoplastic. How to classify this tumor is another problem. Most of the tumor cells were very anaplastic and spindle-shaped with erythrocytes located between cells, in a fashion reminiscent of the Kaposi sarcoma. The heart muscle was extensively invaded. Although blood was present in almost all areas, in one block of tissue the tumor cells were polyhedral and more like epithelium. I toyed with the idea that this was an amelanotic melanoma and went so far as to telephone the wife of the patient

*Fienberg, R. Necrotizing granulomatosis and angiitis of lungs and its relationship to chronic pneumonitis of cholesterol type. *Am. J. Path.* 29:913-927, 1953.

yesterday afternoon when I was looking at the slides to see whether her husband had ever had a mole removed; as far as she knew he had not. The alternative diagnosis and one that I favor is a hemangiosarcoma. There are many foci where blood-vessel formation can be made out and where mere vascularity of another type of tumor can be ruled out (Fig. 2).

DR. BLAND: Could a specific, major bleeding point be identified?

DR. CASTLEMAN: No; there was bleeding in every single nodule.

DR. CASS: Was there bleeding in the pericardial sac?

DR. CASTLEMAN: Yes; the pericardial sac was obliterated by organized blood clot as well as fresh blood clot.

A PHYSICIAN: Did you account for the blood in the gastrointestinal tract?

DR. CASTLEMAN: I think it was probably swallowed blood; there were no lesions anywhere except in the chest.

CASE 40192

PRESENTATION OF CASE

A seventy-two-year-old retired policeman was admitted to the hospital because of jaundice, weight loss and back pain.

The patient was apparently well until three months previously, when his appetite diminished and he began to feel unduly weak after mild exertion. Lumbodorsal pain developed and became accentuated on the left side. This pain was dull and aching, occurred in episodes lasting from hours to days and was aggravated by walking and relieved somewhat by bed rest. No nausea or vomiting was associated with the episodes of pain, but he had experienced marked anorexia. About fifteen days later he noticed that the urine was dark. A month before admission generalized pruritus developed and became progressively more severe so that recently it had awakened him at night. Two weeks before admission the stools were noted to be clay colored, and a week later jaundice was observed. Since then jaundice had rapidly deepened.

Episodes of pain apparently were not related to meals; there had been no change in bowel habit. The patient had lost 20 pounds in the three months since the onset of symptoms.

Physical examination showed a well developed and well nourished man who was markedly icteric. The heart and lungs were normal. The liver edge was sharp and palpable one fingerbreadth below the right costal margin. The spleen was not felt, and there were no palpable masses. Peristalsis was normal. The rest of the physical examination was not remarkable.

The temperature, pulse and respirations were normal. The blood pressure was 165 systolic, 85 diastolic.

A urine specimen gave a + test for albumin and a ++ test for bile but was otherwise normal. The urinary urobilinogen was 0.8 Ehrlich units. Examination of the blood demonstrated a hemoglobin of 13.2 gm. per 100 cc., and a white-cell count of 8700. The serum nonprotein nitrogen was 30 mg., the alkaline phosphatase 9.2 units, and the bilirubin 10.0 mg. direct and 13.6 mg. total per 100 cc. The carbon dioxide was 25 milliequiv., the sodium 135 milliequiv., the chloride 97 milliequiv., and the potassium 4.9 milliequiv. per liter. The pH was 7.42, and the prothrombin time 13 seconds (normal, 14 seconds). The fluid drained from the duodenum had a normal viscosity but contained an abnormal amount of calcium bilirubin. A stool specimen was guaiac negative. An electrocardiogram was normal.

A roentgenogram of the chest revealed multiple irregular densities in both apexes, some of which were calcified. The remaining lung fields were clear. A gastrointestinal series demonstrated a normal esophagus. There was some delay in the filling of the antrum and cap, but this may have been due to a small amount of food present in the stomach. The antrum remained narrow through most of the examination but did change in size; the narrowing was considered probably not significant. The duodenal cap was large and was somewhat deformed toward its apex, but no ulcer crater was visualized. There was no evidence of intrinsic or extrinsic disease in the duodenal loop.

In the hospital there was little change in the patient's condition, and a week after admission an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. FRANK C. WHEELOCK*: This case presents the frequently seen problem of the differential diagnosis of obstructive jaundice. Before going farther, may we see the x-ray films?

DR. JOHN F. GIBBONS: Films of the chest show small calcified scars in the apexes of both lungs. The findings do not suggest active pulmonary disease, and the remaining portions of the lungs are clear. The heart is within normal limits. The aorta is moderately tortuous. Both leaves of the diaphragm are at the normal level. A gastrointestinal examination demonstrates no intrinsic disease in the esophagus, stomach or duodenum.

DR. WHEELOCK: There seems to be no lead here to the exact diagnosis.

To take up the history first, anorexia with resulting weight loss, itching followed by clay-colored stools and jaundice are the usual sequence. Exactly what causes the itching is not known, but it may come and persist for long periods before jaundice occurs. The dull lumbodorsal pain on the left side is certainly not characteristic of biliary-tract disease. It could have been due to a cancer of the pancreas; in such cases the prognosis is poor, for the cancer is usually large.

*Assistant in surgery, Massachusetts General Hospital.

The physical examination is interesting primarily because no gall bladder was felt. Courvoisier, in 1890, described palpable enlargement of the gall bladder in cases of cancer of the pancreas. A dilated gall bladder is not present as a rule when the common duct is obstructed by stones due to scarring and contraction. There are exceptions, of course, to this "law," but it is very useful.

If the liver edge was felt as being "sharp" we can assume that the patient was well relaxed and not too fat. In this event, if the gall bladder had been large, it should have been palpated. In seeking a large gall bladder, one should look tangentially across the abdomen since it can sometimes be seen as a dome-shaped elevation as the patient breathes deeply. I have seen a large gall bladder in at least one patient when it was almost impossible to palpate. At any rate this patient had no palpable gall bladder, and this fact is against carcinoma of the head of the pancreas as the cause of the jaundice.

The laboratory work is consistent with obstruction of the biliary tree, with a low urobilinogen in the urine and an elevated alkaline phosphatase. The presence of abnormal amounts of calcium bilirubin in the duodenal drainage is indicative of stones in the gall bladder or ductal system in about 90 per cent of the cases. The negative stool guaiac test helps little. If there had been a tumor of the ampulla itself or penetration of the duodenum by a carcinoma of the pancreas, one would expect an occasionally positive guaiac test. The x-ray films showed no sign of carcinoma in the head of the pancreas, which, if present, sometimes enlarges the duodenal loop or indents the second portion of the duodenum.

What, then, are the possible diagnoses? Stones in the common duct constitute a good possibility. They certainly may occur with little or no pain. I think a three-month history of anorexia, with jaundice only appearing after eleven weeks of illness, is slow progression for stones, however.

Carcinoma of the head of the pancreas is another likely condition. Against it are the absence of an enlarged gall bladder, the absence of any x-ray signs of an enlarged pancreas, a negative stool guaiac test and the lack of signs of pancreatic malfunction such as fatty or loose stools. In favor of this diagnosis is the characteristic history. Carcinoma of the pancreas may coincide with the presence of gallstones so if I choose to make this my diagnosis, the presence of calcium bilirubin crystals should not deter me too much.

Chronic pancreatitis may cause jaundice, but one would expect a longer history, more pain and an enlarged pancreas. It seems most unlikely.

Carcinoma of the antral end of the stomach or elsewhere in the gastrointestinal tract can metastasize to the porta hepatis and cause obstruction of the common or hepatic duct. We have no evidence of trouble outside the biliary tract, so this seems unlikely.

Carcinoma of the common hepatic duct can produce jaundice of this type without an enlarged gall bladder and without deforming the duodenum.

The length of the history together with the marked weight loss at the age of seventy-two makes me believe that cancer was probably present in the picture somewhere. It is also hard for me to disregard the calcium bilirubin in the duodenum. The diagnosis that seems to allow all the factors to fit best together seems to me to be carcinoma of the gall bladder extending into the hepatic duct. This disease occurs almost exclusively in a gall bladder containing stones and does not usually result in a palpable gall bladder. The only thing I am sure of is that this patient needed an operation.

DR. WINFIELD S. MORGAN: Dr. Green, will you tell us the opinion on the ward?

DR. THOMAS H. GREEN: We tended to favor a diagnosis of carcinoma of the head of the pancreas, for, as Dr. Wheelock has observed, the duration and character of the symptoms in a man of this age seemed more in keeping with this disease than with other causes of obstructive jaundice. The absence of a palpable gall bladder and the finding of calcium bilirubin crystals in the duodenal aspirations, however, warranted our placing common-duct stone as a strong second choice.

CLINICAL DIAGNOSIS

Carcinoma of head of pancreas.
?Common-duct stone.

DR. FRANK C. WHEELOCK'S DIAGNOSES

Carcinoma of gall bladder extending into hepatic duct.
Cholelithiasis.

ANATOMICAL DIAGNOSES

Choledocholithiasis.
Chronic cholecystitis and cholelithiasis.
Bile stasis of liver.

PATHOLOGICAL DISCUSSION

DR. GREEN: At operation the liver was slightly enlarged and presented the gross appearance of a mild biliary cirrhosis. The gall bladder was indeed small and fibrotic, and contained multiple stones of various sizes. The pancreas was perhaps somewhat firmer than usual but was otherwise normal to palpation. When the common duct was exposed it was found to be markedly dilated and thickened, and a stone was felt immediately below the cystic-duct entrance. This calculus was removed, and no others were found on careful exploration of the duct. After dilatation of the ampulla cholecystectomy was carried out, and a liver biopsy obtained.

DR. MORGAN: Grossly, the gall bladder, as received in the laboratory, was small, fibrotic and filled with many faceted brown-black gallstones measuring up to 0.6 cm. in greatest dimension. Microscopically, it showed the typical changes of chronic cholecystitis. The biopsy of liver revealed a few lymphocytes in the portal areas, with slight increase of portal connective tissue, but no definite evidence of biliary cirrhosis. There was, however, a moderate amount of bile stasis. This degree of change in the liver is in accord with the clinical history of relatively recent obstruction that appeared about two and a half months before admission rather than recurrent jaundice over many years, in which case the development of biliary cirrhosis would have been more likely.

DR. GREEN: Postoperatively, the jaundice cleared rapidly, and convalescence was uneventful. A cholangiogram done before discharge outlined a normal-appearing biliary tree, with no evidence of residual stones.

MASSACHUSETTS PHYSICIANS ART SOCIETY

26. Warrior's Head

Hammered Copper by
JACOB W. HITE, M.D.

Medical Staff, Massachusetts Women's Hospital

The New England Journal of Medicine

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JOINT STATEMENT ON VENEREAL DISEASE

THE highest rate of infection with syphilis to be recorded for the population of the United States since 1920 occurred in 1943,[1] when in the midst of World War II it reached 447 per 100,000 population. During the years 1944 through 1947 the rate was cut substantially, doubtless owing to the advent of penicillin and vigorous efforts to determine contacts—reported to average between 3 and 4 persons per infected patient. In the postwar period Congress, in 1947-48, appropriated $17,000,000 for venereal-disease control, with the tangible result that during the next five years rates for syphilis were more than halved, from 265 in 1947 to 110 per 100,000 population in 1952, and the rate for gonorrhea fell from 284 to 161. In 1953 only $5,000,000 was appropriated, and yet venereal-disease rates continued to fall to 101 per 100,000 for syphilis and 157 for gonorrhea.

The present proposal to reduce this portion of the budget further to $2,300,000 has resulted in a joint statement[2] from the Association of State and Territorial Health Officers, the American Venereal Disease Association and the American Social Hygiene Association deprecating the contemplated cut as penny wise and pound foolish:

> . . . we further urge that the federal government do not now, in a spirit of over-optimism or shortsighted economy, prejudice the eventual success of a program undertaken in high hopes and carried forward with brilliant success. Too early and too abrupt reductions in federal support for venereal disease control have already jeopardized the nation's tremendous investment in money and effort. Much more serious, however, is that further reductions pose a real and serious threat to the health and welfare of the people of our country, for whose protection their government exists.

A detailed argument is presented that loses some of its force because it is too often emotional rather than logical and to the point. Not only do the interested agencies oppose a further cut—for which a sound argument exists—but also they insist on doubling last year's budget in the face of a 10 per cent drop in the rate of syphilis and a steady, although less spectacular, fall in the rate of gonorrhea.

No attempt is made here to deprecate relentless efforts to drive syphilis and gonorrhea the way of tuberculosis, but the assertion that "once again history is repeating itself" is, scientifically, highly doubtful when the rate of syphilis has dropped from 447 to 100 in a decade, during a period when all other indexes of syphilis such as general mortality, infant mortality and first admission to mental hospitals have shown regular improvements. The force of penicillin and new channels of education have been added to the battle. As Smillie[3] says, "For the first time in history, infectious syphilis can be handled effectively and rendered non-infectious in short order." The joint statement would have been stronger if it had included more of specific budgetary difficulties and justifications rather than so many over-all generalities about venereal disease.

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WELLCOME RESEARCH LIBRARY

THE Wellcome Research Library of the Royal Society of Medicine is, in a number of respects, analogous to the Boston Medical Library. They are comparable in size, the British institution containing 250,000 and

the American establishment 220,000 volumes, 156,000 pamphlets and 1100 current periodicals. The London library has annually 40,000 to 50,000 visitors and a circulation to the provinces of 80,000 items; the Boston repository of medical learning has an annual attendance of 16,000 and a circulation of 45,000 items. The new library of the Royal Society, the gift of the Wellcome Foundation, was completed in the fall and opened on December 4; the extended facilities of the Boston Medical Library, made possible by the contributions of over 1200 subscribers, will become available this summer.

The Royal Society of Medicine, young as British institutions go, was the result of a fusion some fifty years ago of the Royal Medical and Chirurgical Society of London and various specialty groups. As the Society has gradually become "a centre of meeting for medical men concerned with the advancement of medical knowledge by research, communication and discussion," so its library has come to occupy a position of central importance in the Society's services, and the most distinguished in England if not, indeed, in all of Europe.

The now expanded home of the Royal Society at 1 Wimpole St. was erected in 1911. Originally intended as a four-story structure, it was restricted in the building to three floors because of financial stringency, but with architectural provision for the fourth floor when and if it might be required. The saving of £5,000 was in that way effected.

Libraries have a tendency to grow at an ever-accelerating pace unless with advancing years they become also increasingly selective. By the early 1940's—despite the War and partly because of it, since the Medical Services of the Allied Armies were making greater demands on the Society than it could meet—it had become necessary to consider completing the building, largely to provide additional book space. Estimates made at that time called for an expenditure of £50,000, of which between £2,000 and £3,000 was raised from the fellows of the Society.

Again in 1948 a figure for construction was obtained, this time of £88,000, which was nearly met two years later by a grant from the Wellcome Trust of £80,000. This generous offer was shortly increased by an additional gift of £45,000, ensuring the success of the project.

Much interesting information about the Society and its new Library was presented in the account of the opening ceremonies, published in the January number of the Society's *Proceedings*. On that occasion, Sir Henry Dale, chairman of the Wellcome Trustees and a former president of the Society, gave a historical account of the enterprise.

The story of the creation of the Wellcome Foundation, Ltd., by the late Sir Henry Wellcome was told in the *Journal* of December 3, 1953, in an editorial commenting on the centennial of Sir Henry's birth. As that happy event had taken place at Almond, Wisconsin, in 1853, the top floor of the Royal Society of Medicine containing the Wellcome Research Library may be considered in one pleasing sense an American contribution.

MINOR VICES

THE current scarcity of coffee, with its resultant higher prices and the threats of housewives to boycott the product, brings to mind that not too many years ago the drinking of coffee was regarded as a minor vice. However, the younger generation of today denies ever having heard that, and many young adults now boast of their prowess in imbibing huge quantities of the cup that raises the blood pressure without inebriating.

Granata* recently presented new data on the pharmacologic effects of a cup of coffee. One hundred and ten persons, some of them children and some of them adults, were the subjects of this study. The pulse and respiratory rates and blood pressure were determined, and electrocardiograms taken first before the tests, then after the drinking of a cup of Kaffee Hag (96 per cent of the caffeine removed from the bean), again after a cup of coffee and finally after another cup of Kaffee Hag. The tests clearly showed that the pharmacologic effects of coffee were due to its caffeine content, each cup of coffee containing 0.1 to 0.2 gm. of caffeine and the Kaffee Hag containing only traces.

The pharmacologic reaction of children was similar to that of the adults. The most striking effects of coffee were in the blood-pressure findings. In every subject the systolic pressure rose at least 10 mm. and the diastolic pressure at least 5 mm. The rise in 7 cases of glomerulonephritis was 30 to 50 mm. The blood pressure of a child with diabetes rose from 100 systolic, 60 diastolic, to 210 systolic, 100 diastolic, and that of one with a pheochromocytoma from 120 systolic, 50 diastolic, to 240 systolic, 120 diastolic. In some subjects rhythmic disturbances in the heart action were observed, tachycardia and extrasystoles being frequent. Rises in pulse and respirations were not so consistent or marked as the rise in the blood pressure.

It is reasonable to classify the coffee-drinking, or caffeine, "habit" with the other drug habits—opiates, alcohol, barbiturates and nicotine. One has the coffee habit if he cannot do without his breakfast cup, or two or more, the mid-morning cup, with each meal, in between times and whenever facing stress. The victim will admit that it is bad—rather proudly—but tries to justify it; he usually will not and possibly cannot overcome it. Perhaps the best approach to the problem is to impress children more strongly with the desirability of avoiding coffee and escaping the habit.

*Granata, G. Sperimentazione della reactività cardiovascolare infantile a caffè normale e caffè privato di caffeina. *Minerva paediat.* 5:915-922, 1953.

It is pertinent to recall that the popular "cola" drinks get their appeal from their caffeine content; should not "cola" addiction also be classed as drug addiction? There are tea addicts, too. (But New Englanders do not have to rely on tea for their fluid supply, as the inhabitants of some European countries where water is polluted by coliform organisms.) Perhaps, after all, food addiction is the most devastating of the minor vices. As Masefield so tersely phrased it, "A carelessness of life and beauty marks the glutton, the idler, and the fool. . ."

"THE PRECOCIOUS BABY"

It seems not unlikely that W. S. Gilbert had been given somewhere a briefing on progeria before he wrote "The Precocious Baby" (to be sung to the air of the Whistling Oyster). This elegant verse, as all students of *The Bab Ballads* know, concerned the marital exploit of a septuagenarian in wooing and winning a youthful partner—and the result of the union:

> The cunning old blade,
> Though rather decayed,
> He married a beautiful, beautiful maid.

The eventual product of conception turned out to be a sophisticated young rascal from the start, and his talents were not slow in developing still further. Born with "a weed in his mouth and a glass in his eye" not unlike Charlie (not Joe) McCarthy, he presented somewhat of a social and moral problem to all with whom he came in contact. Fortunately the perplexities associated with his career were not prolonged:

> He early determined to marry and wive
> For better or worse
> With his elderly nurse —
> Which the poor little boy didn't live to contrive:
> His health didn't thrive —
> No longer alive,
> He died an enfeebled old dotard at five!

So much for this classic example of precocious wedlock, contemplated if not contrived. A generally unrelated subject, even if one capable of evoking certain spurious analogies, is the recent report emanating from the Metropolitan Life Insurance Company's corps of statisticians on early fatherhood accomplished. According to this release it appears that more and more American males at tenderer and tenderer years are assuming the responsibilities of marriage and of parenthood. This early paternalistic trend, however, is assumed to be rather the result of normally burgeoning manhood than of any demonstrated progeric factor.

The problem has not yet become one of adolescence, twenty-five years having been selected as an arbitrary base line prior to which fatherhood may be considered as premature; it appears that the number of fathers below this age had already increased by 55 per cent between 1940 and 1952. With the span of life elongating at its present rate and the first quarter century becoming a smaller and smaller proportion of it in relation to the whole, this period may yet be viewed as falling inside the compass of extreme youth.

Consultations in difficult and protracted cases are many times of infinite advantage to both physician and patient, when conducted in a frank, honest and courteous manner.

Boston M. & S. J., *May 17, 1854*

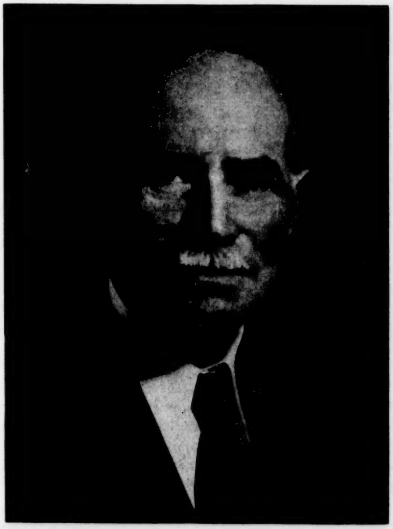
MASSACHUSETTS MEDICAL SOCIETY

CLARENCE GUY LANE, M.D.

1882-1954

Clarence Guy Lane, M.D., died on March 12, 1954. He was returning from a cruise to the Caribbean.

Dr. Lane was born in Billerica, Massachusetts, on October 21, 1882, the son of Dr. Albert Clarence and



Estelle J. Lane. He received his early education in the public schools of Woburn, Massachusetts. His

academic education was completed at Harvard University in 1905. In 1908 he received his degree from Harvard Medical School, *cum laude*. He became a member of the Alpha Omega Alpha Society in 1907. His postgraduate training was received at the Worcester City Hospital, after which he joined his father in the practice of general medicine. In World War I he joined the medical corps of the armed forces as a first lieutenant and was discharged as a captain in 1919. Soon after the war he developed an interest in dermatology, studied with Dr. George McKee, of New York, and became proficient in x-ray therapy of the skin. Long a member of the Department of Dermatology at the Massachusetts General Hospital he became its chief in 1936, returning to the board of consultants ten years later. Dr. Lane was appointed assistant in dermatology at the Harvard Medical School in 1925, was promoted to the head of the department with the title of Lecturer in 1936 and became clinical professor in 1939, a post that he held until his retirement. He had served on the editorial board of the *New England Journal of Medicine* since 1932 as well as on the board of the *Archives of Dermatology and Syphilology*.

Medical education was one of Guy Lane's great interests. He played an important part in the organization of the American Board of Dermatology and Syphilology; he was its first secretary and its president from 1945 to 1946. He served on the advisory board for medical specialties from 1941 to 1943.

He was a member of the American Medical Association, American Dermatological Association, American Academy of Dermatology, New England Dermatological Society, Massachusetts Medical Society and Boston Dermatological Club. He was secretary of the American Dermatological Association from 1925 to 1930, its president in 1935-1936 and on its board of directors from 1930 to 1935 and from 1937 to 1945. He was chairman of the Section on Dermatology and Syphilology of the American Medical Association from 1934 to 1935. He also served as secretary and president of the New England Dermatological Society. In 1949 he gave the Distinguished Lecture before the section on Dermatology and Syphilology of the American Medical Association. He was elected president of the American Academy of Dermatology for 1952-1953. In 1952-1953 he served as president of the Boston Dermatological Club.

Dr. Lane was the author of numerous articles on dermatology and syphilis and was an accepted authority on industrial dermatoses and x-ray therapy of the skin. He was the first to describe the cause of chromoblastomycosis in 1915. He was editor of Vol. 10, *Dermatology and Syphilis*, of the Practitioners Library in 1936.

He was consultant to many hospitals in New England. He was an honorary member of the British Association of Dermatology and a corresponding member of the French Society of Dermatology.

Dr. Lane was a dynamic and tireless worker and took seriously every part of his work, no matter how trivial. He was an excellent administrator. His life was a full one that included other interests such as the study of fingerprinting, which, like his medical work, he took seriously. He was a warm and genial personality and his friends among colleagues and the lay community are numerous and widespread over many American and European countries. By them he is sadly missed, and in his more immediate circle he has left an irreparable gap. It is not doubted that he would have given more active years of service to his fellow men if he had been spared.

He leaves his widow, Mary Rivers Lane, who was a great inspiration and help, and a son, Robert.

DEATHS

BADGER—George S. C. Badger, M.D., of Boston, died on April 28. He was in his eighty-fourth year.

Dr. Badger received his degree from Harvard Medical School in 1897. He was formerly physician-in-chief, New England Baptist Hospital; school physician, Boston; president, Boston Tuberculosis Association; and a member of the staffs of the Massachusetts General Hospital and Harvard Medical School.

He is survived by his widow, a daughter, a son and seven grandchildren.

FOUNTAIN — Oliver R. Fountain, M.D., of Rowley, died on April 24. He was in his seventy-fifth year.

Dr. Fountain received his degree from Harvard Medical School in 1903.

He is survived by his widow.

HOWARD — Joseph F. Howard, M.D., of Lawrence, died on April 1. He was in his seventy-ninth year.

Dr. Howard received his degree from Harvard Medical School in 1899. He was a fellow of the American Medical Association.

He is survived by his widow, three daughters, a granddaughter and several nieces and nephews.

HUBBARD — Edward R. Hubbard, M.D., of Berwyn, Pennsylvania (formerly of Taunton), died on April 23. He was in his fiftieth year.

Dr. Hubbard received his degree from McGill University Faculty of Medicine in 1931. He was a member of the New England Obstetrical and Gynecological Society and a fellow of the American Medical Association and the American College of Surgeons.

He is survived by his widow, a daughter, a son, three sisters and two brothers.

MILLS — Chester R. Mills, M.D., of Needham and Boston, died on April 12. He was in his sixty-first year.

Dr. Mills received his degree from Harvard Medical School in 1919. He was chief of the Oral Service, Boston City and Glover Memorial hospitals, and a member of the staff of Tufts College Medical School, a fellow of the American Medical Association and the American Academy of Ophthalmology and Oto-Laryngology and a member of the New England Oto-Laryngological Society.

He is survived by his widow, a daughter, a son and a sister.

POMEROY — Harris S. Pomeroy, of Peabody, died on April 20. He was in his seventy-ninth year.

Dr. Pomeroy received his degree from New York University College of Medicine in 1900. He was formerly a member of the staff of the J. B. Thomas Hospital in Peabody.

He is survived by his widow.

PRATT — Ernest F. Pratt, M.D., of Lowell, died on March 18. He was in his sixty-first year.

Dr. Pratt received his degree from Middlesex University School of Medicine in 1921. He was formerly physician for the Lowell Catholic Charitable Bureau.

He is survived by his widow, a daughter and a grandson.

BOSTON MEDICAL LIBRARY

SERVICE DURING RENOVATIONS

The work on the completion of the stacks is expected to begin about May 1 and will not be finished for six to eight months. During this period the Library plans to renovate completely the Periodical Room. These changes, of necessity, will cause some curtailment of service and delay in furnishing books and periodicals. The material that has been temporarily moved out of the Library to the storage warehouse, to be returned when the stacks are completed, is mostly secondary or unusual sets. If it is called for during the renovation, it cannot be made available. It is hoped that the dislocation will not seriously interfere with any scholarly work that is being undertaken.

The current periodicals will be made available, probably in Holmes Hall, but there may have to be some slight curtailment of the numbers that are easily accessible.

Every effort will be made by the staff to make the Library as useful as possible during this transition period.

HENRY R. VIETS, M.D., *Librarian*
JAMES F. BALLARD, *Director*

CORRESPONDENCE

CLARIFICATION

To the Editor: I should like to offer a few clarifying remarks regarding my recent article, entitled "Mycosis Fungoides: Report of a Case Terminating in Myelogenous Leukemia," which appeared in the February 11 issue of the *Journal*.

My attention has been called to several minor discrepancies in Table 1 of the paper. Apparently, the implication is that the patient received 24, 630 r unfiltered as a total accumulated dose to the entire cutaneous surface. This, of course, is not technically correct and, as presented, appears misleading since one should not summate the various amounts of radiation given to different body regions. Also, the amount of radiation delivered to each body section by spray is a sixth of the totals indicated, or 1220 r spray accumulated incident dose anteriorly and a similar amount posteriorly, and 1015 r spray to the right and left lateral aspects of the body. This comes from the fact that in spray treatment the body was divided into three separate sections for each position, each section receiving 30 r per treatment in the initial stages and 45 r per treatment in the later stages of his disease.

Nevertheless, the patient did receive a considerable amount of ionizing radiation, which was necessary to control the skin disease and to postpone his death.

JOHN E. LEDONNE, M.D.
Beverly, Massachusetts

WRONG PAGE

To the Editor: It should be called to the attention of the *Journal's* readers, especially in the local area, that the Dr. Emil Page who was named in the newspapers as one of the physicians involved in the recent fee-splitting episode in East Boston is not Dr. Emil Paige, of Marblehead, a highly respected fellow of the Society.

W. RICHARD OHLER, M.D.
Boston

BOOK REVIEW

The Allergic Child. By Harry Swartz, M.D. 8°, cloth, 297 pp. New York: Coward-McCann, Incorporated, 1954. $3.95.

It is obvious that the author of this book has a thorough knowledge of allergy, that he is a sincere scholar and that he has given a great deal of thought to what one might call the "philosophy of allergy." The book has in it much valuable information with most of which no allergist would disagree. The author, however, has shot far over the heads of most parents—much of what he has to say is suitable only for parents who have the same type of mind that he has.

The first chapter, entitled "From New Born to Human Being," begins with the following sentence: "Just as the womb is the theater where evolution of man from a single celled animal is acted out in quick telescoped, but continuous scenes, so the home is the womb of society, where the evolution of man from a jungle animal to an integrated social unit is acted out in a compressed and highly complicated play." The rest of this chapter is in the same vein. It is doubtful whether a young mother will read it and if she will get any good out of it if she does.

Another chapter, on the subject "The Over-all Treatment of the Allergic Child," opens as follows: "As was pointed out earlier, the basic mechanism of the allergic reaction lies in the liability of the energy pattern within cells. Logically, therefore, the most efficient treatment of allergy should deal with such volatility, attempting to make it more stable."

These two quotations are typical of the book, which in the reviewer's opinion, is quite unsuited to serve as a "help and guide to parents," the purpose for which it is intended.

LEWIS W. HILL, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Design and Operation of Septic Tanks: Third European Seminar for Sanitary Engineers. 8°, paper, 122 pp., with illustrations. Geneva: World Health Organization, 1953. $1.50. *(World Health Organization Monograph Series* No. 18.)

Twelve physicians and sanitarians participated in the seminar, at which the various aspects of sewage disposal were discussed. There is an interesting article on the effect of treatment on bacteria count.

Water, Electrolyte and Acid-Base Balance: Normal and pathologic physiology as a basis for therapy. By Harry F. Weisberg, M.D., assistant professor of clinical pathology and of clinical medicine, Chicago Medical School, clinical chemist, Mount Sinai Medical Research Foundation and Hospital, and associate attending physician, Cook County and Mount Sinai hospitals, Chicago. 8°, cloth, 245 pp., with 29 tables. Baltimore: Williams and Wilkins, 1953. $5.00.

This monograph, intended as a review and source book, is based on a seminar given by the author in 1950 at the Mount Sinai Hospital, Chicago, and published in the *Bulletin* of the hospital. There is a bibliography of 398 references, a glossary of abbreviations and symbols, and a good index. The book is well published and should be in all medical libraries.

A Primer of Cardiology. By George E. Burch, M.D., Henderson Professor of Medicine, Tulane University of Louisiana School of Medicine, physician-in-chief, Charity Hospital, consultant in cardiovascular diseases, Ochsner Clinic, and visiting physician, Touro Infirmary, New Orleans. Second edition. 8°, cloth, 339 pp., with 214 illustrations. Philadelphia: Lea and Febiger, 1953. $5.50.

This primer is intended for the medical student and physician interested in an introduction to cardiology. The text in this second edition has been revised and brought up to date. New material and illustrations have been incorporated, and some subjects have been expanded. There is a good index, and the publishing is excellent.

Reason and Unreason in Psychological Medicine. By E. B. Strauss, M.A., D.M., (Oxon.), F.R.C.P., physician for psychologic medicine, St. Bartholomew's Hospital, lecturer in psychologic medicine, St. Bartholomew's Hospital Medical College (University of London), and physician for psychologic medicine, North Middlesex Hospital. With a foreword by Sir Russell Brain, M.A., D.M. (Oxon.), P.R.C.P., physician, London Hospital, and physician, Maida Vale Hospital. 8°, cloth, 55 pp. Springfield, Illinois: Charles C Thomas, 1953. $2.25.

In 1952 Dr. Strauss delivered the Croonian Lectures before the Royal College of Physicians, London. They were entitled "The Concept of Causality" and "Causality and Psychological Medicine." To them has been added "Quo vadimus?"—an address that Dr. Strauss delivered as chairman of the Medical Section of the British Psychological Society in 1946. The small book, printed in Great Britain, is well published.

Leibesübungen mit Körperbeschädigten: Ein Lehr- und Arbeitsbuch für Körperbehinderte und ihre Betreuer. Vol. 2. By Hans Lorenzen. With a supplement on medicine in athletics by Dr. med. habil. H. Hoske. 8°, paper, 280 pp., with 227 illustrations. Stuttgart: Georg Thieme, 1953. DM 22.50. (Distributed by Grune and Stratton, New York.) *(Arbeit and Gesundheit;* new series, copy 51.)

This volume is devoted to sports and gymnastics. There is a bibliography of 10 pages and a good index.

The Radiology of Bones and Joints: An introduction to the study of tumours and other diseases of bone. By James F. Brailsford, M.D., Ph.D., F.R.C.P., F.I.C.S. (Hon.). Fifth edition. 8°, cloth, 875 pp., with 725 illustrations. Baltimore: Williams and Wilkins, 1953. $19.00.

Dr. Brailsford in this fifth edition of his standard book, first published in 1934, has completely revised the text to include the results of his follow-up investigations of cases of long standing and has also critically reviewed the recent literature on the subject. Nearly 200 illustrations have been added, and a few have been replaced. There is a bibliography of 18 pages and a good index. The printing was done in Great Britain, and the publishing is excellent. The book is recommended to all interested persons and to all medical libraries.

Cure Your Nerves Yourself. By Louis E. Bisch, M.D., Ph.D. 8°, cloth, 247 pp., New York: Wilfred Funk, Incorporated, 1953. $3.50.

Dr. Bisch, who has been a practicing psychiatrist for forty-two years, has held a number of teaching and advisory positions in his field. This new popular book is the seventh in a series on psychiatric subjects or mental hygiene.

Synopsis of Pediatrics. By John Zahorsky, M.D. Assisted by T. S. Zahorsky, M.D., senior instructor in pediatrics, St. Louis University School of Medicine, and assistant pediatrician to the St. Mary's Group of Hospitals. Sixth edition. 12°, cloth, 470 pp., with 158 illustrations and 9 color plates. St. Louis: C. V. Mosby Company, 1953. $6.00.

Managing Your Coronary. By William A. Brams, M.D. 8°, cloth, 158 pp., with illustrations by Hertha Furth. Philadelphia: J. B. Lippincott Company, 1953. $2.95.

This small book was written for the patient with coronary-artery disease. It discusses the symptoms, the course of the disease, its treatment and living with the disorder. A chapter is devoted to modern research on heart conditions.

Medical Jurisprudence. By I. Gordon, M.B., Ch.B. (Cape Town), senior government pathologist, Union Health Department, Durban; R. Turner, M.B., Ch.B., D.P.H. (Cape Town), senior government pathologist, Union Health Department, Cape Town, and professor of medical jurisprudence, University of Cape Town; and T. W. Price, Ph.D., M.A., LL.B. (Cantab.), B.A., LL.B. (South Africa), advocate of the Supreme Court of South Africa, of Gray's Inn, barrister-at-law, and professor of Roman-Dutch law, University of Cape Town. Third edition. 8°, cloth, 944 pp., with 143 illustrations. Edinburgh: E. and S. Livingstone, Limited, 1953. $13.50. (Distributed by Williams and Wilkins, Baltimore, Maryland.)

In this new edition a book last published in 1945 as a manual for students has been expanded into a work for the medical and legal professions. The medical parts of the original manual have been revised, and sections and chapters have been rewritten. Naturally, the legal aspects conform to the practice and statutes of the Union of South Africa and Southern Rhodesia. Otherwise, the book constitutes a comprehensive treatise on medicolegal medicine. There are unusual and interesting chapters on unprofessional conduct, contracts and medical insurance, malpractice and the public duties of the medical practitioner. There is a good index, and the publishing is excellent. The book should be in all collections on the subject.

The Size and Growth of Tissue Cells. By Joseph G. Hoffman, Ph.D., director of Cancer Research, Roswell Park Memorial Institute, research professor of biophysics, University of Buffalo School of Medicine, and consultant, Los Alamos Scientific Laboratory, University of California, Los Alamos, New Mexico. 8°, cloth, 102 pp., with 13 illustrations and 5 tables. Springfield, Illinois: Charles C Thomas, 1953. $4.00. (Publication No. 172, *American Lecture Series.)*

This monograph presents a survey of the size and growth of tissue cells from the work of Hermann Lebert in 1851 to the present time. There is a bibliography of 115 references and author and subject indexes.

NOTICES

Dr. Herbert I. Posin announces the removal of his office for the practice of psychiatry to 25 Windsor Road, Brookline 46, Massachusetts.

Dr. John Boda announces the opening of an office for the general practice of medicine and eye examination on Route 40, Lowell Road, Groton, Massachusetts.

Dr. Cyril A. Bergman announces the opening of an office for the practice of pediatrics at 50 Oliver Street, Fitchburg, Massachusetts.

SOUTH END MEDICAL CLUB

A meeting of the South End Medical Club will be held at the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on May 25 at 12 noon. Dr. Eugene E. Record, Massachusetts General Hospital and New England Peabody Home for Crippled Children, will speak on the subject "The Amputee Patient."

MASSACHUSETTS SCHOOL PHYSICIANS' ASSOCIATION

The annual meeting of the Massachusetts School Physicians' Association will be held in Parlor B of the Hotel Statler, Boston, on Wednesday, May 19, from 2:15 to 4 p.m. Dr. Kenneth E. Macleod, director, Nashoba Associated Boards of Health, will speak on the topic "The Union Regional Health Program" at 2:15, and Dr. William Berenberg, Harvard Medical School, on the subject "Early Recognition and Management of Cerebral Palsy" at 3 p.m. The business meeting will be held at 4 p.m. Nonmember physicians and school nurses are invited to the lectures.

PAN-AMERICAN CONGRESSES OF PEDIATRICS

The fourth Pan-American Congress of Pediatrics, the fourth South American Congress of Pediatrics and the eighth Brazilian Day Session on Puericulture and Pediatrics will be held in conjunction with the fourth-centennial celebration of Sao Paulo, Brazil, in that city from August 1 to 7. Further information may be obtained from the General Secretary, Rua Anita Garibaldi, 43 — apto. 701 — Copacabana, Rio de Janeiro, Brazil.

SOCIETY MEETINGS AND CONFERENCES

May 17–21. Examination, American Board of Otolaryngology. Hotel Statler and Massachusetts Eye and Ear Infirmary.
May 17–23. National Tuberculosis Association. Page 663, issue of April 15.
May 18–26. Consultation Clinics for Crippled Children. Page 705, issue of April 22.
May 18–20. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston. Page 740, issue of April 29.
May 19. Massachusetts School Physicians' Association. Annual Meeting. Page 849.
May 19. Massachusetts Medical Society. Section of Industrial Health. Page 791, issue of May 6.
May 25. Sigma Xi Lecture. Page 792, issue of May 6.
May 25. South End Medical Club. Page 849.
May 27 and 28. New York Surgical Division of International College of Surgeons. Page 585, issue of April 1.
May 27–29. American College of Cardiology. Page 585, issue of April 1.
May 31–June 3. American Urological Association. Page xvii, issue of July 23.
June 5 and 6. International Association for the Study of the Bronchi. Page 400, issue of March 4.
June 11–13. American Electroencephalographic Society. Page 748, issue of April 29.
June 13–17. American Society of Medical Technologists. Page 444, issue of March 11.
June 14–16. American Neurological Association. Page 540, issue of March 25.
June 15–18. Medical Library Association. Page 491, issue of March 18.
June 17–19. American Geriatrics Society. Page 266, issue of February 11.
June 17–21. Pan American Congress of Ophthalmology. Page 540, issue of March 25.
June 19 and 20. Society for Investigative Dermatology. Page 540, issue of March 25.
June 23. Tufts Medical Alumni AMA Dinner. Page 585, issue of April 1.
July 22 and 23. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.
July 23–29. International Cancer Congress. Page 914, issue of November 26.
July 26–31. International Congress of Gynecology and Obstetrics. Page 400, issue of March 4.
August 1–7. Pan-American Congresses of Pediatrics. Notice above.
August 17–20. Argentine Congress of Thoracic Surgery. Page 708, issue of April 22.
September 6–10. International Poliomyelitis Congress. Page 399, issue of March 4.
September 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.
September 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.
September 16–18. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.
October 8 and 9. Academy of Psychosomatic Medicine. Page 748, issue of April 29.
October 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.
December 13–17. Congress of Obstetrics and Gynecology. Page 748, issue of April 29.
June 21–25, 1955. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, MAY 20

THURSDAY, MAY 20

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
11:00 a.m. Thoracic Conference. Surgical Treatment of Angina Pectoris. Dr. Harrison Black. Main Amphitheater, Peter Bent Brigham Hospital.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, MAY 21

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Drs. Proger, Hayman, McCombs, Astwood and other members of the Medical Staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, MAY 22

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Auditorium, New England Center Hospital.

MONDAY, MAY 24

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Foot Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Medical Clinical Pathology Conference. Discussion by Dr. James Dow. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*4:00–5:00 p.m. Surgical Pathology Conference. Stearns Auditorium, New England Center Hospital.
*7:00–9:00 p.m. Combined Anesthesia Resident Training Program. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

TUESDAY, MAY 25

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
12:00 m. South End Medical Club. The Amputee Patient. Dr. Eugene E. Record. Boston Tuberculosis Association, 554 Columbus Avenue.
*12:00 m. Pediatric Grand Rounds. Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Endocrine Conference. Dr. Astwood. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
*12:30–1:30 p.m. Medical Journal Club. Cafeteria, New England Deaconess Hospital.
*4:00–5:30 p.m. Anesthesia Teaching Conference. Dr. Etsten. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*8:00 p.m. Sigma Xi Lecture. Psychiatry, Its Scope and Research Potentials. Dr. Harry C. Solomon. Allston Burr Lecture Hall, Harvard University, Broadway and Quincy streets, Cambridge.

WEDNESDAY, MAY 26

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
11:00 a.m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Conferences: Department of Neurology, Neurosurgery and Psychiatry. Drs. Sullivan, Bertram Selverstone and Hope. Stearns Auditorium, New England Center Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*5:00–6:00 p.m. Cancer Society Telecast. Treatment of Patients with Advanced Cancer of the Thyroid: Psychiatry and Analgesia. Drs. Raymond W. Houde and Arthur M. Sutherland. Children's Cancer Research Center, 35 Binney Street.
*7:30–9:30 p.m. Lahey Clinic Lecture. The Problem of Common Duct Strictures. Medical Aspects. Dr. John Norcross. Surgical Aspects. Dr. Richard B. Cattell. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.